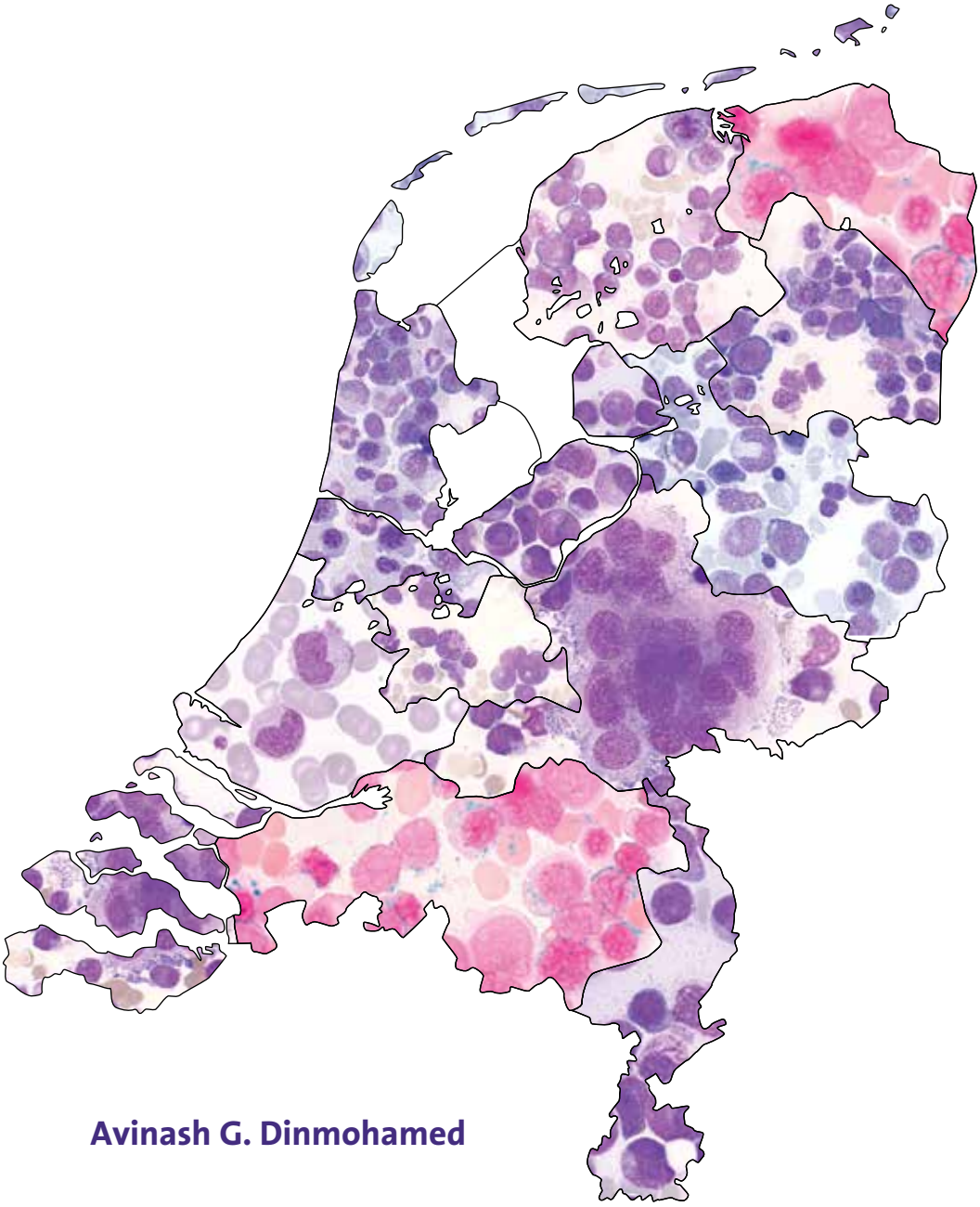
The True Face of Myelodysplastic Syndromes and Related Neoplasms in the Netherlands: Studies based on population-based registries



Avinash G. Dinmohamed

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De ware aard van myelodysplastische syndromen en gerelateerde maligniteiten in Nederland: Studies gebaseerd op populatie-gebaseerde registraties

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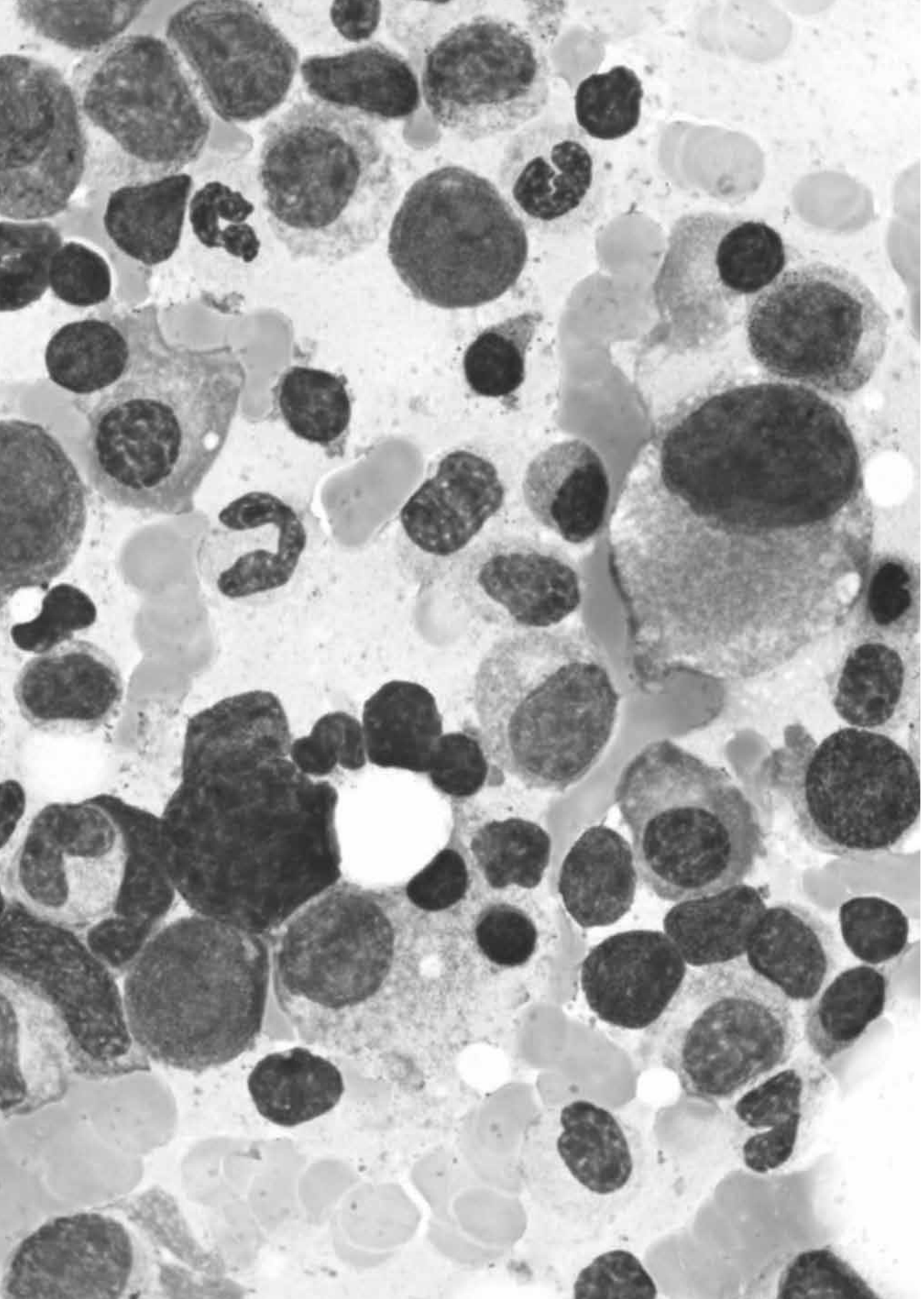


General introduction

1

HEMATOLOGICAL MALIGNANCIES

Hematological malignancies comprise a diverse group of tumors that affect the blood, bone marrow and lymph nodes, and account for around 8% of all malignancies diagnosed annually in the Netherlands.[1] They originate from either of the two main blood cell lineages, that is, myeloid or lymphoid cell lineages. Published in 2008, the fourth edition of the World Health Organization (WHO) classification of Tumors of Hematopoietic and Lymphoid Tissues, better known as the WHO 2008 classification of hematological malignancies, recognizes 11 main categories of hematological malignancies, each with several subtypes.[2] In general, lymphoid malignancies (e.g. lymphomas and myeloma) are more common than myeloid malignancies (e.g. acute and chronic myeloid leukemias).[3] More specifically, the overall annual age-standardized incidence rates in Europe were 24.5 per 100,000 persons for lymphoid malignancies and 7.6 per 100,000 persons for myeloid malignancies.[3] Despite differences in incidence rates, they generally affect older adults.[3] Moreover, almost 60% of all patients with hematological malignancies are over the age of 65 at diagnosis in the Netherlands.[1] Due to the ageing population, the incidence and prevalence of hematological malignancies will rise, making these broad spectrums of diseases an important public health concern.

Hematological malignancies of myeloid origin that predominantly affect the elderly include, but are not limited to, myelodysplastic syndromes (MDS), chronic myelomonocytic leukemia (CMML) and acute myeloid leukemia (AML). These myeloid malignancies are related, albeit distinct, disease entities and are diagnosed in around 65, 70 and 45% of people above the age of 70, respectively.[1] Despite that they are frequently diagnosed among older adults, they are commonly excluded, or underrepresented in clinical trials.[4] Therefore, findings from clinical trials may not be generalizable to the entire older patient population. As a result, optimal diagnostic and treatment approaches for this elderly population are based on insufficient evidence and remain controversial. In addition, clinical trials do not and cannot provide a complete picture of the overall characteristics of patients at the population level.

The focus in this thesis is set on the epidemiologic delineation of MDS and CMML in the Netherlands to provide insight into the burden of these malignancies at the population level. The following sections provide an introduction to both malignancies. Seeing that one chapter in this thesis is specifically dedicated to delineate the clinical epidemiology of AML in the Netherlands, a concise clinical overview on AML is provided as well.

MYELODYSPLASTIC SYNDROMES

Incidence

At the turn of the century, the WHO formally classified MDS as a malignant neoplasm, and consequently MDS became a reportable malignancy to cancer registries as from 2001.[5] Since then, there are only a few large studies that have provided representative epidemiologic data on the incidence of MDS in the general population.[3,6-12] Most of these studies are based on information gained from either regional or nationwide population-based cancer registries,[3,6-9,11,12] which are instruments that are the gold standard for cancer surveillance in the general population.[13] The scarcity of large epidemiologic studies in MDS may in part be explained by the possible difficulties in ascertaining MDS cases due to the lack of well-established cancer registries, and changes in classification criteria of MDS over time.

It follows that the few available large epidemiologic studies in MDS have consistently reported that the overall age-standardized incidence rate of MDS is around 3.0 to 4.0 per 100,000 persons in Western countries.[3,6-12] Of note, in Asian countries such as China and Japan, the incidence of MDS is lower than that in Western countries, namely around 1.0 to 1.5 per 100,000 persons.[14,15] The reasons underlying the ethnic/geographic differences are not completely understood. The lower incidence in Asian countries may be related to ethnicity and/or environmental and life style factors. Turning to Western countries, the incidence of MDS increases progressively after the age of 60, thereby making it a disease that primarily affects older adults, as the median age at diagnosis is typically around 75 years.[3,6-12] Like most malignancies, MDS has an overall male predominance.[3,6-12] There is an exception, however, as a specific subtype of MDS has a female predominance, namely MDS with an interstitial deletion of the long arm of chromosome 5—better known as MDS associated with isolated del(5q).[16]

Although not considered as an instrument for cancer surveillance, a few epidemiologic studies in MDS were recently conducted using information gained from large medical claims databases.[17,18] These studies, which were conducted in the United States (U.S.) and Australia, suggested that MDS might be underreported in population-based cancer registries. Depending on the methodology used for case definition in these medical claim-based studies, the overall incidence of MDS was approximately two to four times higher than the incidence reported by cancer registries. Several hypotheses to explain the possible reasons for underreporting were brought forward in these studies. First, the cancer registries of the U.S. and Australia do not (or rarely) register cases that were diagnosed in the outpatient setting. Secondly, both cancer registries do not include MDS secondary to a primary malignancy. Lastly, both cancer registries only include cases that were confirmed through histopathology and/or cytomorphology, whereas medical claims databases include cases irrespective of the diagnostic procedure (e.g. based on peripheral blood cytopenias only). The latter point might be a concern, as it is not possible to establish a diagnosis of MDS without histopathological and/or cytomorphological conformation.[19] Despite that well-established cancer registries provide the most reliable data on MDS incidence within a well-defined population, it cannot be denied that the incidence of MDS may be underreported.

Etiology

Apart from demographic factors such as old age and male sex,[20] the etiology of MDS is poorly understood and only known in approximately 15% of cases.[21] Cytotoxic therapy and/or radiation therapy for a previous neoplastic or non-neoplastic disease are established risk factors for MDS—better known as therapy-related or secondary MDS.[22-26] To a lesser extent, several occupational (e.g. exposure to benzene and other solvents,[27-31] and radiation[32]), environmental (e.g. non-occupational benzene exposure by tobacco smoking[27,28,30-36]) and life style factors (e.g. alcohol consumption[27,29,36] and hair dye use[27,29,30,32,36]) have been implicated to be potentially involved in the etiology of MDS.[20] Also, it follows that genetic susceptibility may contribute to the development of MDS. First, patients with inherited bone marrow failure syndromes, such as congenital neutropenias and Fanconi anemia, have a high predisposition to develop MDS.[37] Second, although very rare, familial cases of MDS have been described in the literature (e.g. familial platelet disorder with propensity to myeloid malignancy).[38] Last, polymorphism in genes that are involved in xenobiotic metabolism might enhance susceptibility to MDS due to the impaired detoxification of carcinogens.[39]

Biology

MDS constitute a diverse spectrum of clonal hematopoietic stem cell disorders characterized by hematopoietic insufficiency resulting in refractory cytopenias affecting one or more cell lineages, that is, erythroid, myeloid and megakaryocytic cell lineages.[21] In approximately a third of patients, the disease will transform to AML.[40] The exact pathogenesis of MDS is not fully understood but involves processes including either or both cytogenetic changes and gene mutations, and immune dysregulation.[41] Hematopoietic insufficiency in patients with MDS results from an aberrant susceptibility of clonal myeloid progenitor cells to apoptosis, which attributes to cytopenias.[42] Factors that have been implicated in the apoptotic process of myeloid progenitor cells include abnormal signaling of cytokines in these cells (e.g. TGF-ß[43] and TNF-α[44]) as well as an altered immune response in T cells (e.g. decrease of regulatory T cells[45]). Leukemic progression in MDS is presumed to be facilitated through an alteration from apoptosis to proliferation of clonal myeloid progenitor cells. More specifically, an increased numbers of regulatory

T cells may be implicated in facilitating this process, mainly by suppressing the autoimmune response against myeloid precursor cells, thereby facilitating clonal expansion and subsequent progression of MDS.[46-51]

Several recurrent somatic gene mutations have recently been characterized that may be involved in the pathogenesis of MDS. The list of genetic mutations include genes coding for epigenetic regulators involved in methylation (e.g. *DNMT3A*[52]) or hydroxymethylation (e.g. *TET2*[53] and *IDHI1/2*[54]) of cytosines present in CpG island, and histone modification (e.g. *ASXL1*[55] and *EZH2*[56]). The list also includes mutations in oncogenes and tumor suppressor genes (e.g. *RUNX1*,[56] *TP53*[56,57] and *ETV6*[56]), as well as in genes constituting pivotal elements of the RNA-splicing machinery (e.g. *SF3B1*,[58] *SRSF2*,[59] *U2AF1*[60] and *ZRSR2*[59]). In general, mutations in those genes can alter gene expression patterns as well as genomic stability.[61] Around 50 to 90% of patients with MDS harbor at least one gene mutation.[56,62,63] Despite the tremendous efforts made in the past years to identify these genetic aberrations, none of them are diagnostic for MDS, as they can also be found mutated in other myeloid malignancies, such as CMML and AML.[61] Due to the rapidly evolving nature of genetic technologies, novel genetic mutations may be identified in the near future to facilitate genetic characterization of specific MDS subtypes.

Diagnosis

Almost all patients with MDS present with anemia, which is usually, but not exclusively, macrocytic and refractory (i.e. non-regenerative). Isolated neutropenia or thrombocytopenia are rarely observed in MDS at diagnosis. Neutropenia and/or thrombocytopenia usually occur with anemia in one third of patients. Signs and symptoms of MDS are usually non-specific but are generally related to the cell type affected and may involve fatigue or weakness due to the anemia, recurrent (opportunistic) infections due to the neutropenia, and abnormal bruising or bleeding due to the thrombocytopenia or platelet dysfunction.[21] It is not uncommon that patients are diagnosed with MDS during a routine medical check-up, in which an unexplained, asymptomatic anemia is discovered.[64] While the exact proportion of patients diagnosed during a routine medical check-up are as yet not known, approximately 6% of people age 65 or older with unexplained anemia in a large U.S. population-based study had at least macrocytosis, leucopenia or thrombocytopenia, features consistent with the diagnosis of MDS.[65] Unfortunately, in that study, no bone marrow examination was performed to establish (or exclude) the diagnosis of MDS in that particular patient subset.

The diagnosis of MDS heavily relies on subjective morphological evaluation of the peripheral blood and bone marrow, along with cytogenetic analysis of bone marrow cells.[19] These procedures are essential to allow for an accurate diagnosis of MDS. The minimal diagnostic criteria for MDS require that the following two criteria are met to

make the diagnosis of MDS: 1) a marked cytopenia in at least one cell lineage lasting for at least six months and 2) exclusion of other causes of cytopenias and/or dysplasia,[66] such as other myeloid neoplasms (e.g. AML and CMML), nutrition deficiencies (e.g. vitamin B12 and folic acid deficiencies) and autoimmune disorders (e.g. aplastic anemia and systemic lupus).[67] In addition, at least one of the three following criteria should be present: 1) at least 10% dysplasia in one or more myeloid cell lineages in the bone marrow aspirate, 2) cytogenetic aberrancies associated with MDS and 3) bone marrow blast percentages between 5% and 19%.[66]

Dysplasia of hematopoietic cell lineages and the percentage of bone marrow blasts should be assessed in both the peripheral blood and bone marrow aspirate to allow for a correct classification of MDS.[19] In addition, ring sideroblasts are enumerated in the bone marrow aspirate and necessary for classification as well.[19] The bone marrow biopsy is crucial for the assessment of fibrosis and $CD34^+$ cell clusters, which has prognostic value in MDS.[19,68] Also, the bone marrow biopsy may provide useful in cases where the bone marrow aspirate is of insufficient quality due to marrow fibrosis (i.e. dry tap) or hypocellular.[19]

Cytogenetic analysis of bone marrow cells is important to determine the clonality of suspected MDS. In addition, specific cytogenetics aberrancies have strong prognostic value in MDS and,[69] in certain instances, may provide evidence of MDS in the absence of definitive morphologic characteristics.[66,70] Cytogenetic aberrancies are detected in approximately 50% of patients with MDS at diagnosis.[69,71,72] The most frequent single cytogenetic aberrancies include del(5q), monosomy 7, del(7q) and del(20q).[69,71,72] Complex cytogenetics, that is, at least 3 cytogenetic aberrancies, are also detected, albeit less frequent than single cytogenetic aberrancies.[69] A complex karyotype is almost exclusively associated with very poor prognosis.[69] Cytogenetic aberrancies are more abundantly observed in patients with excess of marrow blasts (i.e. 5 to 19% blasts).[72]

Other diagnostic techniques such as fluorescence in situ hybridization (FISH),[19] flow cytometry immunophenotyping[73-75] and molecular genetics[56,62,63] are recognized as valuable tools in the diagnosis of MDS, especially in cases where the diagnosis remains uncertain after standard diagnostic techniques.[19] Currently, FISH and flow cytometry immunophenotyping are recommended diagnostic approaches, whereas molecular screening can as yet not be recommended on a routine basis.[19] In cases were cytogenetic analysis failed using standard G-banding techniques (e.g. due to insufficient metaphases), FISH can be utilized to detect specific cytogenetic aberrancies by using specific probe sets targeted to, for example, del(5q) or del(7q).[19] Flow cytometry immunophenotyping according to the methodology devised by the International Flow Cytometry Working Group within the European LeukemiaNet is recommended as co-criteria in the minimal diagnostic work-up of MDS in cases where MDS-related criteria are not met (i.e. less

than 10% dysplasia in myeloid cell lineages in the bone marrow, absence of typical MDS-related cytogenetic abnormalities and less than 5% bone marrow blasts).[19,76-78] Future studies will be needed to delineate how these abovementioned diagnostic techniques should be implemented in routine diagnostic algorithms for MDS in the forthcoming years.

Classification

Established in 1982, the French-American-British (FAB) classification was the first uniform system that classified MDS into five specific subtypes, namely refractory anemia (RA), RA with ring sideroblasts (RARS), RA with excess of blasts (RAEB), RAEB in transformation (RAEB-t) and CMML (Table 1).[79] The FAB classification of MDS heavily relies on subjective morphologic features of the bone marrow, that is, bone marrow dysplasia and percentage of bone marrow blasts. Based on these features, along with information on the number of cytopenias and presence of monocytosis (i.e. >1 x 10^9/L), specific subtypes can be distinguished (Table 1). However, it became apparent over time that, due to the evolving processes of newer clinical, morphologic, biologic and genetic information gained by continuous research efforts, the FAB classification of MDS had some controversies related to its diagnostic criteria. More specifically, certain distinct morphologic and clinical phenotypes could not be classified according to the FAB criteria.[80,81]

Table 1. French-American-British classification of MDS[79]

Subtype	Blood findings	Bone marrow findings
Refractory anemia (RA)	Anemia <1% blasts	Erythroid dysplasia[a,b] <5% blasts <15% ring sideroblasts
Refractory anemia with ring sideroblasts (RARS)	Anemia <1% blasts	Erythroid dysplasia[a,b] <5% blasts ≥15% ring sideroblasts
Refractory anemia with excess of blasts (RAEB)	1 to 3 cytopenias <5% blasts	Dysplasia in ≥1 lineages[a] 5%-19% blasts
Refractory anemia with excess of blasts in transformation (RAEB-t)	1 to 3 cytopenias ≥5% blasts	Dysplasia in ≥1 lineages[a] 20-29% blasts
Chronic myelomonocytic leukemia (CMML)	1 to 3 cytopenias <5% blasts ≥1 x 10^9/L monocytes	Dysplasia in ≥1 lineages[a] <20% blasts

[a] dysplasia is defined as dysplasia in ≥10% of the cells in a particular cell lineage.
[b] granulocytic and megakaryocytic dysplasia may also occur

As a result, the FAB classification of MDS was revised in 2001 by a panel of field experts in neoplastic hematology under the auspices of the WHO.[5] The popular term of the revised classification system is the WHO 2001 classification, which also includes the revision of other hematological malignancies.[82] The FAB criteria for MDS was the backbone for the revised classification, and therefore, for a large part, still relies on morphology. The WHO 2001 classification for hematological malignancies was refined in 2008 (i.e. the WHO 2008 classification), and, for MDS, only included minor revisions as compared to the WHO 2001 classification.[70] An outline of the WHO 2008 classification of MDS is presented in Table 2.

Table 2. WHO 2008 classification of MDS[223]

Subtype	Blood findings	Bone marrow findings
Refractory cytopenias with unilineage dysplasia (RCUD): - refractory anemia (RA); - refractory neutropenia (RN); - refractory thrombocytopenia (RT)	1 or 2 cytopenias[a] <1% blasts[b]	Dysplasia in ≥10% of cells in 1 cell lineage <5% blasts <15% ring sideroblasts
Refractory anemia with ring sideroblasts (RARS)	Anemia No blasts	Dyserythropoiesis <5% blasts ≥15% ring sideroblasts
Refractory cytopenia with multilineage dysplasia (RCMD)	1 to 3 cytopenias <1% blasts[b] No Auer rods <1 x 10^9/L monocytes	Dysplasia in ≥10% of cells in ≥2 cell lineages <5% blasts No Auer rods With or without 15% ring sideroblasts
Refractory anemia with excess of blasts-1 (RAEB-1)	1 to 3 cytopenias <5% blasts No Auer rods <1 x 10^9/L monocytes	Dysplasia in ≥10% of cells in ≥1 cell lineages 5%-9% blasts No Auer rods
Refractory anemia with excess of blasts-2 (RAEB-2)	1 to 3 cytopenias 5-19% blasts ± Auer rods[c] <1 x 10^9/L monocytes	Dysplasia in ≥10% of cells in ≥1 cell lineages 10%-19% blasts ± Auer rods[c]
Myelodysplastic syndromes unclassifiable (MDS-U)	1 to 3 cytopenias <1% blasts[b]	Unequivocal dysplasia in <10% of cells in ≥1 cell lineages + cytogenetic aberrancy considered as presumptive evidence for a MDS diagnosis <5% blasts
MDS associated with isolated del(5q)	Anemia Normal to increased platelet count <1% blasts	Dysplasia in ≥1 lineages <20% blasts

[a] Two cytopenias may occasionally be observed. Cases which present with pancytopenia should be classified as MDS-U. [b] Whenever the bone marrow blast percentage is <5%, but there are 2 to 4% blasts in the peripheral blood, the diagnosis of REAB-1 should be made. Cases of RCUD and RCMD with 1% blasts in the peripheral blood are classified as MDS-U. [c] Cases which present with Auer rods and <5% blasts in the peripheral blood and <10% in the bone marrow should be classified as RAEB-2.

The major differences between the FAB and the WHO classification are as follows. First, and most important, the blast threshold for the diagnosis of MDS was lowered from 30 to 20% in the peripheral blood or bone marrow. Accordingly, patients with ≥20% blasts are diagnosed as AML. Moreover, patients with REAB-t according to the FAB classification, that is, those with 20 to 29% blasts in the bone marrow, are currently, but not exclusively, classified within a specific category of AML, namely AML with MDS-related changes. This category is defined by the absence of specific recurrent genetic abnormalities of AML and the presence of at least one of the following features: (i) dysplasia in at least 50% of the cells in at least two bone marrow cell lineages, (ii) MDS-related cytogenetic abnormalities, or (iii) prior MDS or MDS/MPN. Of note, the latter two features only have prognostic relevance.[83] Second, the significance of dysplasia in two or three cell lineages (i.e. multilineage dysplasia) was recognized, because particular MDS phenotypes with multilineage dysplasia and <5% blasts in the bone marrow could not be classified according to the FAB criteria. Hence, the category of refractory cytopenias with multilineage dysplasia (RCMD) was introduced. The former FAB categories of RA and RARS were retained, but only slightly revised to have only erythroid dysplasia (i.e. unilineage dysplasia). Also, a similar concept of unilineage dysplasia was extended to encompass patients with exclusively granulocytic or megakaryocytic dysplasia, which were termed as refractory neutropenia (RN) and refractory thrombocytopenia (RT), respectively. To encompass entities with unilineage dysplasia (i.e. RA, RN and RT), the category of refractory cytopenia with unilineage dysplasia (RCUD) was introduced. In addition, it has been shown that most patients with unilineage dysplasia have superior survival than patients with multilineage dysplasia.[84] Third, a specific cytogenetic abnormality, that is an isolated del(5q), was recognized to be diagnostic for a specific MDS subtype, seeing its distinct morphologic and clinical phenotype. Fourth, REAB was separated into two categories, namely RAEB-1 and -2, based on the percentage of blasts in the peripheral blood and bone marrow. This separation was necessary as it became clear that both categories have prognostic implications, in which REAB-2 is the highest stage of MDS. Of note, the presence of Auer rods in blasts upstages any MDS subtype into REAB-2. Fifth, CMML was retracted as a specific MDS subtype, because there was controversy whether CMML was a myelodysplastic or myeloproliferative neoplasm. Therefore, it was included in a new category of myelodysplastic/myeloproliferative neoplasms. Taken together, MDS, CMML and AML are related malignancies of myeloid origin; however, it has become obvious over time that they are distinct disease entities.

The diagnosis and classification of MDS can be challenging in patients with mild cytopenias and/or minimal dysplastic changes in the bone marrow. In these patients, idiopathic cytopenia of undetermined significance (ICUS) or idiopathic dysplasia of undetermined significance (ICUS) can be considered.[85] Both conditions may progress

to overt MDS (or AML) over time; however, the natural history of these conditions are currently poorly understood, mainly due to their rarity.[86] Very recently, the terms clonal hematopoiesis of indeterminate potetial (CHIP) and clonal cytopenias of undetermined significance (CCUS) were introduced.[87] The former term is used to describe individuals who have a hematological malignancy-associated somatic mutation in either the peripheral blood or marrow, but lacking definitive criteria associated with a particular hematological malignancy.[87] In two recent large genome-wide association studies, the prevalence of CHIP among septuagenarians, who were unselected for hematologic phenotypes at inclusion, was approximately 10%.[88,89] Generally, the prevalence of CHIP increases continuously with age.[88,89] What was interesting was that the rate of progression from CHIP towards a hematological malignancy was less than 1% per year.[87] This finding suggest that molecular screening alone is currently insufficient to establish a definitive diagnosis of MDS. As for the term CCUS, it is used to describe ICUS patients (that is, those with unexplained cytopenias) with clonal hematopoiesis.[87] In a recent study, it has been shown that approximately 30% of patients with ICUS harbor MDS-associated somatic mutations, especially ICUS patients with some degree of dysplasia.[90] Interestingly, these so called CCUS patients showed similar variant allele frequencies, median age and blood counts as compared to patients with definitive MDS. Collectively, the finding of somatic mutations indicative of clonal hematopoiesis—with or without unexplained cytopenias—is, at present, not sufficient for the diagnosis of MDS or any other hematological malignancy.

Prognosis

The life expectancy of patients with MDS is quite variable, ranging, on average, from around 6 months to 6 years, and is mainly dependent on the MDS subtype,[91] along with other disease- (e.g. number[40] and degree[92] of cytopenias and cytogenetics[69]) and patient-related characteristics (e.g. age[92] and comorbidity[93]). Because of the heterogeneity in clinical outcome, even between patients with the same disease subtype,[84,91] accurate prognostication is deemed mandatory as a key element of patient care.[19]

Published in 1997, the International Prognostic Scoring System (IPSS) is nowadays still considered the reference standard for predicting the prognosis among newly diagnosed, untreated patients with MDS.[40] In addition, it is still used for the design and analysis of clinical trials, drug approval purposes, and, most importantly, treatment decision-making in MDS. The IPSS considers three independent, disease-related parameters, namely the percentage of bone marrow blast, cytogenetic abnormalities and the number of cytopenias present at the time of diagnosis, which were weighted as presented in Table 3.[40] Based on these parameters, patients can be separated into four distinctive risk categories (that is, low, intermediate-1, intermediate-2 or high risk), each with meaningful differences in overall survival and time to leukemic progression (Table 3).[40] The IPSS is a

relatively simple scoring system, because the parameters of the IPSS should be readily available, as they are essential for the diagnostic work-up of MDS. Despite that the IPSS is based on the FAB classification of MDS, it is also applicable among patients with MDS who are classified according to the WHO criteria.[94]

Table 3. IPSS prognostic score values and clinical outcomes for MDS[40]

	Score value				
Prognostic variable	**0**	**0.5**	**1.0**	**1.5**	**2.0**
Bone marrow blasts, %	<5	5-10	-	11-20	21-30
Cytogenetics[a]	Good	Intermediate	Poor		
No. of cytopenias[b]	0-1	2-3			
IPSS total score	**0**	**0.5-1.0**		**1.5-2.0**	**≥2.5**
IPSS risk category	Low	Intermediate-1		Intermediate-2	High
Proportion of patients	33%	38%		22%	7%
Median overall survival, years	5.7	3.5		1.2	0.4
25% AML evaluation, years	9.4	3.3		1.1	0.2

[a] The cytogenetic subgroup 'Good' includes normal karyotype, -Y, del(5q), del(20q); 'Poor' includes a complex karyotype (i.e. ≥3 cytogenetic aberrancies), or chromosome 7 aberrancies; and 'Intermediate' includes cytogenetic aberrancies not otherwise specified by the IPSS. [b] Cytopenias are defined as follows: hemoglobin level <6.2 mmol/L, absolute neutrophil count <1.8 x 10^9/L and platelet count <100x 10^9/L.

In 2007, a scoring system was developed that specifically takes into account the diagnostic classification of MDS according to the WHO classification, better known as the WHO-classification-based Prognostic Scoring System (WPSS).[95] In addition, the WPSS includes IPSS-based cytogenetic stratification and transfusion dependency status. Despite the prognostic capability of the WPSS and its subsequent revisions,[96,97] it has not achieved widespread acceptance like the IPSS.

More recently, in 2012, the existing prognostic parameters of the widely accepted IPSS were revised (hereafter referred to as the IPSS-R[92]) by defining new thresholds and weights for cytopenias, bone marrow blast counts and cytogenetics, and, more importantly, by including additional cytogenetic abnormalities, each with specific weights (Table 4). Based on these revised parameters, the IPSS-R recognizes five distinctive risk groups (Table 5),[92] which allows for more precise prediction of overall survival and leukemic transformation than the initial IPSS (Table 3).[40] In addition, the IPSS-R can upstage lower-risk patients and downstage higher-risk patients according to the initial IPSS.[92] More specifically, as shown in the IPSS-R publication, 27% of patients with low and intermediate-1 risk on the IPSS were shifted to higher-risk IPSS-R categories (i.e. upstaged). The other way around, 18% of patients with intermediate-2 and high risk on the IPSS were shifted to lower-risk IPSS-R categories (i.e. downstaged). Several independent studies have validated the prognostic capability of the IPSS-R.[98-102] Collectively, the IPSS-R may more accurately evaluate patients' prognosis than the initial IPSS.

Other prognostic variables in MDS have demonstrated merit, but are as yet not incorporated in the IPSS(-R), include age,[103-105] performance status,[103,104] comorbidities,[93,101,106,107] ferritin,[104,105] lactate dehydrogenase,[94] β_2-microglobulin,[104] bone marrow fibrosis,[68] immunophenotypes of myeloid progenitor cells[74,108] and specific somatic mutations (e.g. *TP53*, *RUNX1* and *ASXL1*).[56,62,63,109]

Table 4. IPSS-R prognostic score values for MDS[92]

	Score value						
Prognostic variable	**0**	**0.5**	**1.0**	**1.5**	**2.0**	**3**	**4**
Cytogenetics[a]	Very good	-	Good	-	Intermediate	Poor	Very poor
Bone marrow blast, %	≤2	-	>2-<5	-	5-10	>10	-
Hemoglobin, mmol/L	≥6.2	-	5-<6.2	<5	-	-	
Platelets, 10^9/L	≥100	50-<100	<50	-	-	-	-
Neutrophils, 10^9/L	≥0.8	<0.8	-	-	-	-	-

[a] The cytogenetic subgroup 'Very good' includes –Y, del(11q); 'Good' includes normal karyotype, del(20q), del(5q) alone and double, del(12p); 'Intermediate' includes del(7q), +8, i(17q), +19, any other single or double independent clones; 'Poor' includes -7, inv(3)/t(3q)/del(3q), double including -7/del(7q), 3 cytogenetic aberrancies; and "Very poor" includes >3 cytogenetic aberrancies.

Table 5. IPSS-R prognostic risk categories and clinical outcomes for MDS[92]

IPSS-R total score	**≤1.5**	**>1.5-3**	**>3-4.5**	**>4.5-6**	**>6**
IPSS-R risk group	Very low	Low	Intermediate	High	Very high
Proportion of patients	19%	38%	20%	13%	10%
Median overall survival, years	8.8	5.3	3.0	1.6	0.8
25% AML evaluation, years	NR	10.8	3.2	1.4	0.7

Treatment

Most evidence regarding treatment strategies in MDS come from uncontrolled, non-randomized, multicenter studies that included selected patient populations.[19] Therefore, there is insufficient evidence at the moment to support the most appropriate treatment strategy for the vast majority of patients with MDS, especially for older patients. At present, all available results from treatment strategies in MDS arrive from clinical studies that included patients based on risk stratification as per IPSS. Consequently, evidence- and consensus-based treatment algorithms in MDS are still nowadays guided by IPSS risk as recommended by recent Dutch and international clinical practice guidelines.[19,110-113] Therefore, a comprehensive diagnostic approach in MDS is necessary for accurate prognostication, which, in turn, allows for an informed, risk-adapted treatment decision to be made. The following two chapters will briefly touch upon treatment strategies in MDS as recommended by recent Dutch guidelines set by the MDS

working party of the Dutch-Belgian Hemato-Oncology Group (HOVON).[111] That guideline largely follows the recent recommendations set by the European LeukemiaNet for the treatment of MDS.[19]

Treatment of IPSS low and intermediate-1 risk MDS

Treatment of patients with lower-risk MDS (i.e. IPSS low- or intermediate-1 risk) mainly aims to correct cytopenias, especially anemia, so as to improve the quality of life. However, some patients with lower-risk MDS and asymptomatic anemia do not require any specific therapy and should be followed on a regular basis. Whenever there is an indication for treatment among patients with lower-risk MDS, treatment strategies generally consists of red blood cell (RBC) transfusions and iron chelation therapy for RBC transfusion-dependent patients with serum ferritin levels >2000 µg/L. Platelet transfusions are only indicated for thrombocytopenic patients with acute bleeding episodes or undergoing invasive surgical procedures. Antibiotics are indicated for patients with (signs of) infections due to neutropenia. Treatment with erythropoietic-stimulating agents (ESAs), with or witout granulocyte-colony stimulating factor (± G-CSF), may alleviate or correct anemia in patients with lower-risk MDS and are generally considered in first-line.[114] Also, treatment with ESA ± G-CSF may prolong survival and improve quality of life compared to patients who only receive RBC transfusions.[115-118] Patients with low (≤500 U/L) endogenous serum erythropoietin (EPO) and low RBC transfusion needs (<2 RBC units per month) are more likely to respond to ESA ± G-CSF than patients who have high (>500 U/L) endogenous serum EPO and/or higher RBC transfusion needs (≥2 RBC units per month).[119] It has been suggested that patients with lower-risk MDS and an isolated del(5q) have a lower probability to respond to ESA ± G-CSF as opposed to patients with lower-risk MDS patients without del(5q).[120]

More recently, in 2013, following the results of a randomized phase 3 trial (MDS-004),[121] the immunomodulatory agent lenalidomide was registered in the Netherlands for use in lower-risk, transfusion-dependent patients with MDS and an isolated del(5q) who failed or are not eligible for alternative therapies. In around 50% of patients, lenalidomide can induce fast and durable RBC transfusion independency and cytogenetic responses.[121-123] However, when lower-risk patients with an isolated del(5q) have a *TP53* mutation, they seem to confer resistance to lenalidomide and a higher probability of leukemic progression.[124] In the Netherlands, patients with lower-risk MDS—with or without an isolated del(5q)—could be included in the HOVON 89 clinical trial that aimed to assess the efficacy of lenalidomide with or without the addition of ESA ± G-CSF. In August 2015, that clinical trial, which opened for accrual in May 2009, closed for accrual as it reached its target of 200 patients.

In a minor subset of patients, immunosuppressive therapy with anti-thymocyte globulin, with or without cyclosporine, can be considered, mainly among low IPSS risk patients below age 60 with a hypoplastic bone marrow, HLA-DR15 positivity and short transfusion duration.[125-127]

The use of curative treatment, that is, an allogeneic hematopoietic stem cell transplantation (alloHSCT), is usually delayed in lower-risk patients until the disease progresses to higher-risk MDS to maximize life expectancy of these patients.[128] In other words, the risk of transplant-related mortality do not outweigh the relatively low likelihood of excess mortality in lower-risk MDS. However, a subset of patients with lower-risk MDS might be candidates for first-line alloHSCT if they have severe (pan)cytopenia, 5 to 10% bone marrow blasts or poor-risk cytogenetics as per IPSS.

Treatment of IPSS intermediate-2 and high risk MDS

By contrast, as opposed to patients with lower-risk MDS, treatment strategies among patients with higher-risk MDS (i.e. IPSS intermediate-2 or high risk) aim to delay leukemic progression and prolong overall survival. At present, alloHSCT is the only treatment modality with proven curative potential for MDS. Long-term disease-free survival rates are around 40 to 50% after alloHSCT.[129-131] It is currently only recommended for medically fit patients with higher-risk MDS up to age 70.[128,132] However, seeing that around 65% of patients with MDS are above age 70 at diagnosis, the majority is not eligible for alloHSCT. Similarly, patients with severe concomitant comorbidities are usually not offered an alloHSCT, as transplant-related mortality is more likely as compared to patients with mild or no comorbidities who undergo alloHSCT.[133] The use of intensive remission induction chemotherapy before alloHSCT is not clearly settled yet, but is generally offered to patients with >10% blasts in the bone marrow to reduce the tumor burden. Medically fit patients below age 70 who cannot proceed to alloHSCT (e.g. due to lack a suitable stem cell donor) can be offered remission induction chemotherapy followed by post-remission chemotherapy after attaining complete remission, provided that they have >10% blasts in the bone marrow without poor-risk cytogenetics as per IPSS.

Until recently, no specific therapeutic agent was approved in the Netherlands for the treatment of patients with higher-risk MDS who are not eligible for alloHSCT. However, in 2009, following the results of a randomized phase 3 clinical trial (AZA-001 trial), the first therapeutic agent was approved in the Netherlands for the treatment of transplant-ineligible patients with higher-risk MDS, namely the hypomethylating agent azacitidine.[134] Results of that trial clearly demonstrated the efficacy of azacitidine in higher-risk MDS, as it significantly prolonged overall survival compared to conventional care regimens, including best supportive care (BSC) only, low-dose cytarabine (LDAC) or intensive chemotherapy (median overall survival, 24.5 vs. 15.0 months). The survival advantage of azacitidine was independent of age, bone marrow blast percentage and karyotype. Interestingly, patients with chromosome 7 abnormalities, who usually respond poorly to LDAC and intensive chemotherapy, had improved survival with

azacitidine. Of note, *post hoc* analysis by treatment group on overall survival revealed that azacitidine was superior to BSC only or LDAC. Overall survival was, however, similar between azacitidine and intensive chemotherapy. Furthermore, azacitidine delayed leukemic progression compared to BSC only, but not compared to LDAC or intensive chemotherapy. A first response with azacitidine was achieved by 6 cycles in 91% of patients, which suggest that long-term treatment with azacitidine is necessary for a treatment effect to become evident.[135] Interestingly, patients who achieved a hematologic improvement in the absence of a complete or partial remission also enjoy improved survival with azacitidine.[136]

Decitabine is another hypomethylating agent with a slightly different mechanisms of action than azacitidine. However, in MDS, decitabine did not demonstrate the same efficacy as azacitidine in terms of prolonging overall survival over BSC only.[137,138] Therefore, decitabine is not registered in the Netherlands and other European countries for the treatment of higher-risk MDS. The differences in efficacy between decitabine and azacitidine could be attributed to the administration route (intravenous[137,138] vs. subcutaneous[134]) and the duration of treatment. As for the latter, decitabine was given for a median of 3 cycles in one study[137] and a median of 4 cycles in another study,[138] while azacitidine was administered for a median of 9 treatment cycles.[134]

CHRONIC MYELOMONOCYTIC LEUKEMIA

Incidence and etiology

The exact incidence of CMML is not well documented in part due to changes in its diagnostic classification over time. As CMML is characterized by features of both MDS and MPN, previous studies might have either grouped CMML with MPN (e.g. chronic myeloid leukemia—a specific MPN entity) or considered CMML as MDS. Currently, there are only a few population-based studies that specifically assessed the incidence of CMML.[7-11] Data from these studies showed that CMML is a very rare malignancy that primarily affects older adults and males. More specifically, the overall age-standardized incidence rate is approximately 0.2 to 0.4 per 100,000 persons and increases progressively after age of 70; the median age at diagnosis is around 75 years. CMML is uncommon among patients below age 50.

The etiology of CMML is unknown and difficult to study seeing its rarity, but may arise in approximately 10% of patients due to previous cytotoxic therapy and/or radiation therapy for an antecedent neoplastic or non-neoplastic disease.[139] As for familial cases of CMML, they are extremely rare, which is not unexpected since CMML is very rare by itself, and only recently described in the setting of familial thrombocytopenias.[140]

Biology

The biology of CMML is currently not fully understood but it certainly involves processes including either or both cytogenetic changes and gene mutations.[141] CMML is a clonal hematopoietic stem cell disorder characterized by features of both MDS and MPN, such as cytopenias, leukocytosis, monocytosis and an increased propensity for leukemic progression.[142] In approximately 30% of patients with CMML, chromosomal abnormalities can be detected, with trisomy 8 being the most common and del(5q) the most uncommon.[143,144] More recently, in approximately 90% of patients with CMML, a spectrum of somatic mutations was discovered that might contribute to disease initiation and subsequent progression of CMML.[62,145-149] These mutations, however, are not exclusively mutated in CMML, as they can also be found in MDS,[62,63,148] but there were some notable differences between CMML and MDS. First, the frequency of commonly mutated genes differ between CMML and MDS.[40,41,123] For example, *SRSF2*, an important gene of the spliceosome, is more frequently mutated in CMML than in MDS (approximately 40% vs. 10%).[63,148] Second, fewer genes are mutated in CMML compared to MDS.[58] In other words, CMML is, at the molecular level, less heterogeneous than MDS. Third, the clonal architecture of CMML is distinct from those with MDS, mainly due to different order of acquisition and clonal hierarchy of somatic mutations.[150] Taken together, these findings support the notion that CMML and MDS are distinct biologic entities.

Diagnosis and classification

CMML is seen as a diagnostic challenge because the diagnosis relies on subjective morphological evaluation of the peripheral blood and bone marrow, along with cytogenetic testing, in patients with unexplained cytopenia and monocytosis.[151] A hallmark that distinguishes CMML from MDS is the requirement of a persistent peripheral blood monocytosis in CMML, that is, an absolute monocyte count above 1 x 10^9/L.[5,151] However, other causes of monocytosis should be excluded, such as other MPNs (e.g. chronic myeloid leukemia—CML), auto-immune disorders (e.g. rheumatoid arthritis and systemic lupus), as well as bacterial, viral and protozoan infections.[152] Signs and symptoms of CMML are non-specific, but are similar to those in MDS (e.g. fatigue due to anemia). In addition, due to the myeloproliferative characteristics of CMML, patients may experience symptoms related to splenomegaly, which is palpable in approximately 25 to 50% of patients.[153-155]

Before the introduction of the WHO 2001 classification, CMML was considered a distinct subtype of MDS according to the FAB classification of MDS.[79] According to the FAB criteria, CMML can be divided into a myelodysplastic variant (CMML-MD) if the white blood cell (WBC) count is <13 x10^9/L and a myeloproliferative variant (CMML-MP) if the

WBC count is ≥13 x10^9/L.[156] Due to the controversy as to whether CMML is primarily a myelodysplastic or a myeloproliferative disease,[157] CMML was eliminated as a MDS subtype and has been classified into the category of myelodysplastic/myeloproliferative (MDS/MPN) diseases as of 2001, when the WHO 2001 classification of hematological malignancies was published.[5] The name of this category was changed to MDS/MPN neoplasms when the WHO 2008 classification of hematological malignancies was published.[70] Other entities that are included in this category include, atypical chronic myeloid leukemia (aCML), juvenile myelomonocytic leukemia (JMML) and MDS/MPN unclassifiable (MDS/MPN-U). In addition, RARS and thrombocytosis (RARS-T) is included in this category as a provisional entity.

The diagnostic criteria of CMML according to the WHO 2008 classification is outlined in Table 6. As in MDS, the diagnosis of CMML requires that blasts should be <20% in the peripheral blood and bone marrow, and dysplasia ≥10% in one or more hematopoietic cell lineages in the bone marrow. However, bone marrow dysplasia is not necessary a prerequisite for the diagnosis of CMML. In addition, and most important, a diagnosis of CMML requires persistent monocytosis. Since the transition from the FAB to the WHO classification, the two CMML variants CMML-MD and CMML-MP were retracted, seeing the rather arbitrary threshold to distinguish both variants.[158] Instead, the WHO classification introduced two categories based on the percentages of blasts in the peripheral blood and bone marrow, which has prognostic value, namely CMML-1 and -2.[159] The threshold for defining monocytosis remained unchanged.

Table 6. WHO 2008 classification of CMML[2]

Diagnostic criteria	
1	Persistent peripheral blood monocytosis, that is, an absolute monocyte count of >1 x 10^9/l
2	No Philadelphia chromosome or *BCR-ABL1* fusion gene
3	No rearrangements of *PDGFRA* or *PDGFRB* (should especially be excluded in cases with eosinophilia)
4	<20% blasts (myeloblasts, monoblasts, and promonocytes) in the peripheral blood or bone marrow
5	At least one of the following requirements:
	a) ≥10% dysplasia in one or more myeloid lineages
	b) An acquired, clonal cytogenetic abnormality is present in the bone marrow cells
	c) A persistent monocytosis for at least 3 months and all other causes of monocytosis have been excluded
Diagnostic subclassification	
CMML-1:	
	<5% blasts in the peripheral blood and <10% blasts in bone marrow
CMML-2:	
	5-19% blasts in the peripheral blood an 10-19% blasts in the bone marrow, or Auer rods irrespective of the blast percentage

The role of cytogenetic assessment in the diagnostic work-up of CMML is essential for multiple reasons. First, cytogenetic analysis may aid in determining the clonality of the disease. Secondly, clonal cytogenetic abnormalities may aid in establishing the diagnosis of CMML in cases where bone marrow dysplasia is absent or minimal. Thirdly, cytogenetic abnormalities have prognostic value. Lastly, cytogenetic analysis is necessary to confirm the absence of a reciprocal translocation between one chromosome 9 and one chromosome 22, which is diagnostic for CML, and rearrangements of *PDGFRA* or *PDGFRB*. Alternatively, molecular testing and/or FISH may assist in excluding these genetic lesions. It is of extreme importance to recognize these distinct genetic lesions, as they are extremely sensitive to the tyrosine kinase inhibitor imatinib.[160,161] Besides, they are specific entities that are not included in the category of MDS/MPN neoplasms. The position of molecular testing in CMML is currently not yet clearly settled, except in the setting to exclude CML (i.e. absence of *BCR/ABL* fusion gene). As for flow cytometry immunophenotyping, it has been recently shown to distinguish between CMML and reactive monocytosis with comparatively high specificity and sensitivity.[162] Its position in the diagnostic work-up of CMML is, however, as yet to be defined.

Prognosis

The life expectancy of patients with CMML is comparatively poor (median overall survival, 13 months[163]), and dependent on several disease- (e.g. bone marrow blast count,[143,164-166] cytogenetics[103,143,166] and molecular genetics[167]) and patient-related factors (e.g. age[103] and performance status[103]). Currently, there are eight prognostic scoring systems available for CMML that have demonstrated merit in a large, independent international dataset.[40,92,103,155,166-169] However, none of them as yet have gained widespread acceptance in clinical practice like the IPSS for MDS. Several reasons can be considered to explain the possible lack of consensus regarding CMML prognostication. First, most scoring systems such as the IPSS,[40] IPSS-R,[92] Global MD Anderson Scoring System[103] and Düsseldorf score[168] were not specifically developed for CMML, but for MDS. Moreover, these scoring systems include prognostic variables that are biased towards MDS. Therefore, they are presumed to be inadequate for the risk stratification of patients with CMML, especially for those with CMML-MP as they were excluded in the development of the IPSS and IPSS-R. Second, all scoring systems that have been proposed for CMML uses different sets of prognostic parameters (e.g. cytogenetics[166] vs. molecular genetics[167]), which are, as yet, not validated in clinical trials. Hence, it is difficult for clinicians to decide which scoring system to use, because evidence- and consensus-based recommendations are lacking to support the value of a particular model over another. In Dutch clinical practice, the molecular-based prognostic scoring system that includes *ASXL1* mutational status is recommended for prognostication and treatment decision-making.[167]

Treatment

Treatment options for patients with CMML usually follows the same treatment principles as for patients with MDS, with the exception of hydroxyurea to control the elevated blood counts in CMML.[151] Moreover, most data on treatment of CMML are extrapolated from the experience and knowledge gained in MDS, as data for their specific use in CMML are scarce.[151] AlloHSCT is the only curative modality for patients with CMML.[170] A recent study of 513 patients with CMML found that 4-year overall survival was 33% after alloHSCT.[170] The vast majority of patients with CMML are, however, not eligible for this procedure as around 70% of patients are above the age of 70 years at diagnosis.[151] For patients who are not eligible for alloHSCT, the therapeutic armamentarium is very limited and includes supportive care (e.g. RBC transfusions), hydroxyurea,[171] ESA without G-CSF,[172] and azacitidine.[134]

Currently, there are no recent randomized phase 3 clinical trials published that specially assessed therapeutic interventions in patients with CMML. Azacitidine was approved in the Netherlands in 2009 for use in CMML-MD with 10 to 19% marrow blast following the result of the phase 3 AZA-001 trial, in which CMML was grouped with MDS and only included a minority of CMML patients (16 of 358 patients in the AZA-001 trial), which were not reported separately.[134] The last phase 3 clinical trial that was specifically conducted among patients with CMML dates from 1996, in which hydroxyurea was compared to etoposide.[171] Several smaller retrospective and phase 2 studies have been completed in CMML; however, these studies have limitations including small sample sizes and lack of a comparator treatment arm.[154,171,173-177] Collectively, current treatment recommendations for CMML are disproportionally based on inadequate scientific evidence; thus they remain largely ill-defined and controversial.[151]

ACUTE MYELOID LEUKEMIA

AML is a heterogeneous clonal hematopoietic stem cell disorder characterized by an abnormal proliferation of immature myeloid progenitor cells in the bone marrow and an arrest in their maturation resulting in ineffective hematopoiesis.[178] Patients with AML commonly present with clinical symptoms such as fatigue, infections and hemorrhages.[178] These symptoms are a direct results of the ineffective hematopoiesis in AML, as functional mature myeloid cells are virtually absent.[178] The disease is very heterogeneous with respect to disease biology (e.g. variable degree of underlying cytogenetic, epigenetic, molecular aberrancies), as well as treatment response and outcome.[178]

Incidence and etiology

The overall age-standardized incidence rate of AML is approximately 3 to 4 per 100,000 in Western countries.[3,11,179,180] It is frequently diagnosed among the elderly as the median age at diagnosis around 65-70 years. AML has a slight male predominance. The etiology of AML is largely unknown in the majority of cases.[181] In approximately 20% of cases, AML occurs after MDS, CMML or MPN (defined as secondary AML).[182] AML after treatment with cytotoxic chemotherapy and/or radiation therapy for other malignant or nonmalignant disorder is defined as therapy-related AML and occurs in around 7% of cases.[182] Furthermore, the development of AML may also be linked to specific environmental and occupational factors, such as ionizing radiation[183] and benzene,[184] and deficient enzymes that detoxify carcinogens.[185] Also, particular congenital disorders, such as Down syndrome[186] and Fanconi anemia,[187] are predisposed to AML.

Diagnosis and classification

Cytomorphology is central to the diagnosis of AML.[188] In 1976, the FAB group published the first system to classify AML into several subtypes, which was based on cytomorphology and cytochemistry.[189] In this classification system, the diagnosis of AML is confirmed when leukemic myeloblasts in the bone marrow exceeds 30%. The current classification system, that is, the WHO 2008 classification, incorporates, next to cytomorphology and cytochemistry, cytogenetic and molecular data, and defines five main categories of AML (Table 7).[70] Since 2001, when the WHO 2001 classification was introduced, the myeloblast threshold to confirm the diagnosis of AML was lowered from 30 to 20%. The diagnosis of AML can also be considered in patients with t(8;21), inv(16) or t(16;16), acute promyelocytic leukemia (APL) with t(15;17), and particular cases of erythroid leukemia, regardless of the myeloblast count. In addition, the WHO 2008 classification includes two new provisional entities based on gene mutations, namely AML with mutated *NPM1* or *CEBPA*.

Table 7. WHO 2008 classification of AML and related precursor neoplasm[70]

AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22); *RUNX1-RUNX1T1*
AML with inv(16)(p13.1q22) *or* t(16;16)(p13.1;q22); *CBFß-MYH11*
AML with t(15;17)(q22;q12); *PML-RARA* and cytogenetic variants (acute promyelocytic leukemia)
AML with t(9;11)(p22;q23); *MLLT3-MLL*
AML with t(6;9)(p23;q34); *DEK-NUP214*
AML with inv(3)(q21q26.2) *or* t(3;3)(q21;q26.2); *RPN1-EVI1*
AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15- MKL1*
Provisional entity: AML with mutated *NPM1*
Provisional entity: AML with mutated *CEBPA*
AML with myelodysplasia-related changes
One of the following: • Previous history of myelodysplastic syndrome (MDS) • MDS-related cytogenetic abnormality • Dysplasia present in > 50% of 2 or more cell lineages Absence of both: • Prior cytotoxic therapy for an unrelated disease • Recurring cytogenetic abnormality as described in AML with recurrent genetic abnormalities
Therapy-related myeloid neoplasms
Includes therapy-related AML, therapy-related MDS and therapy-related MDS/MPN
AML, not otherwise specified
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic and monocytic leukemia
Acute erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Acute leukemias of ambiguous lineage
Acute undifferentiated leukemia
Mixed phenotype acute leukemia with t(9;22)(q31;q34;q11.2); *BCR-ABL1*
Mixed phenotype acute leukemia with t(v;11q23); *MLL* rearranged
Mixed phenotype acute leukemia, B/myeloid or T/myeloid, not otherwise specified
Provisional entity: natural killer (NK) cell lymphoblastic leukemia/lymphoma

Prognosis

The prognosis in AML is generally poor, especially when specific treatment is not promptly initiated after diagnosis.[190,191] Cytogenetic abnormalities at diagnosis, which are detected in approximately 50% of patients, are the strongest prognostic factors to predict response to therapy and survival in AML.[192-197] In addition, they are a mandatory component in the diagnostic work-up of AML, not only for prognostication and treatment-decision making, but also for classification, since particular cytogenetic aberrancies are recognized in the WHO category 'AML with recurrent cytogenetic abnormalities' as specific entities (Table 7).[70,188] Patients are commonly categorized into three major cytogenetic risk groups: favorable, intermediate or adverse. Younger adults with AML more often present with favorable cytogenetic abnormalities (e.g. inv(16), t(16;16) or t(8;21)), whereas these abnormalities are relatively uncommon among older adults.[193,198] Older adults with AML usually present with adverse cytogenetics (e.g. -5, del(5q), -7, del(7q), abnormalities of 11q, 17p, inv(3q), monosomal karyotype or complex karyotypes), which, at least in part, contributes to the poorer prognosis seen among older adults with AML.[193,195-200] The intermediate cytogenetic risk group comprise of entities that are not classified as favorable or adverse (e.g. normal karyotype). Based on clinical trial data including over 1,000 adults with AML (median age of the cohort, 66 years), the proportions of favorable, intermediate and poor-risk cytogenetics were around 7.3, 79.1, and 13.6%, with corresponding 5-year overall survival rates of 34, 13 and 2%, respectively.[193]

Several molecular mutations were recently recognized to be consistently associated with clinical outcome, such as response to therapy and overall survival, in particular among patients without cytogenetic abnormalities, which constitutes around 50% of all AML cases.[201] Gene abnormalities associated with relatively favorable prognosis in AML include *NPM1* mutant without *FLT3-ITD* mutant or bi-allelic *CEBPA* mutant, whereas AML with *EVI1* overexpression or AML with mutations in *ASXL1*, *RUNX1*, *TP53*, or *FLT3-ITD* (bi-allelic or those with high *FLT3-ITD*/*FLT3*-wild type ratios) confer a poor prognosis.[201] Collectively, molecular genetics may enhance current risk stratification models that are primarily based on cytogenetics.[202]

Treatment

The only treatment strategy with a curative potential in AML generally consists of two consecutive phases: remission induction chemotherapy and consolidation therapy consisting of an additional course of intensive chemotherapy, autologous HSCT (autoHSCT) or alloHSCT.[188] The aim of this treatment strategy is to attain and maintain remission, and prevent relapse. The choice of a specific type of consolidation therapy is primarily guided by pre-treatment cytogenetics and molecular genetics, along with chronologic age and comorbidity.[188] Remission induction chemotherapy and consolidation therapy, which is generally designed for and tested in younger patients,

is mostly poorly tolerated by older adults due to excess toxicity and treatment-related mortality.[203] The poor tolerance and increased toxicity may, in part, be explained by various disease-related characteristics (e.g. chemotherapy resistance and adverse risk cytogenetics) as well as patient-related pharmacokinetics (e.g. comorbidities). In recent published clinical trials, long-term survival after intensive therapy could only be attained in around 10% of older[204-206] compared to 40 to 50% in younger adults with AML.[207-211] Patients who are unsuitable candidates for intensive, curative therapy, usually those above age 65, might benefit from less-intensive disease-modifying therapy such as the hypomethylating agents azacitidine[212,213] and decitabine.[214] Treatment with hypomethylating agents may improve survival among selected patients; however, to date, none of these lower-intensity regimens have been shown to be superior to intensive chemotherapy in randomized controlled trials directly comparing intensive chemotherapy to those regimens.

RANDOMIZED CONTROLLED TRIALS AND POPULATION-BASED OBSERVATIONAL STUDIES

Randomized controlled phase 3 clinical trials are the gold standard to assess the efficacy of new therapies. They provide the strongest evidence on treatment efficacy and are critical for the advancement of treatment and changing the outcomes of patients. Treatment guidelines are fundamentally established following the results from randomized controlled phase 3 trials. The strength of randomized controlled trials (RCTs) depends on the random allocation (randomization) of patients into either the experimental treatment group or the control group. In addition, they require patients to meet with stringent inclusion criteria that dictate patient eligibility in a trial. These processes allow for a homogeneous study population in terms of equal distribution of baseline characteristics (e.g. prognostic factors associated with outcome) and an equal chance for each patient to be allocated to either the experimental or control group. As such, the only difference between the two groups is their exposure to the experimental treatment. In other words, RCTs have high internal validity, which, however, comes at the price of diminished generalizability as a result of stringent inclusion and exclusion criteria. Therefore, treatment efficacy and survival estimates from clinical trials may be overestimated, thereby impeding the broad applicability of trial results to the vast majority of patients in routine clinical practice (i.e. they have low external validity).[215,216] In general, patients with older age and/or greater comorbidity, as well as those who are socioeconomic disadvantaged are underrepresented in RCTs.[217,218] As a result, demographic and clinical characteristics of these patients outside the setting of RCTs are often largely unknown.

It is obvious that other research platforms are needed to address patient populations not studied in RCTs. Population-based registies are one such platform where all patients within a well-defined area are included irrespective of clinical trial participation. In oncology research, the source of information for population-based studies primarily comes from regional or nationwide cancer registries. Also, more recently, large medical claims-based databases are increasingly used for population-based research with or without linking them to cancer registries. The following sections briefly describe the registries established in the Netherlands that are interrogated for the work described in this thesis to delineate the clinical epidemiology of MDS, CMML and AML in the Netherlands.

The nationwide Netherlands Cancer Registry

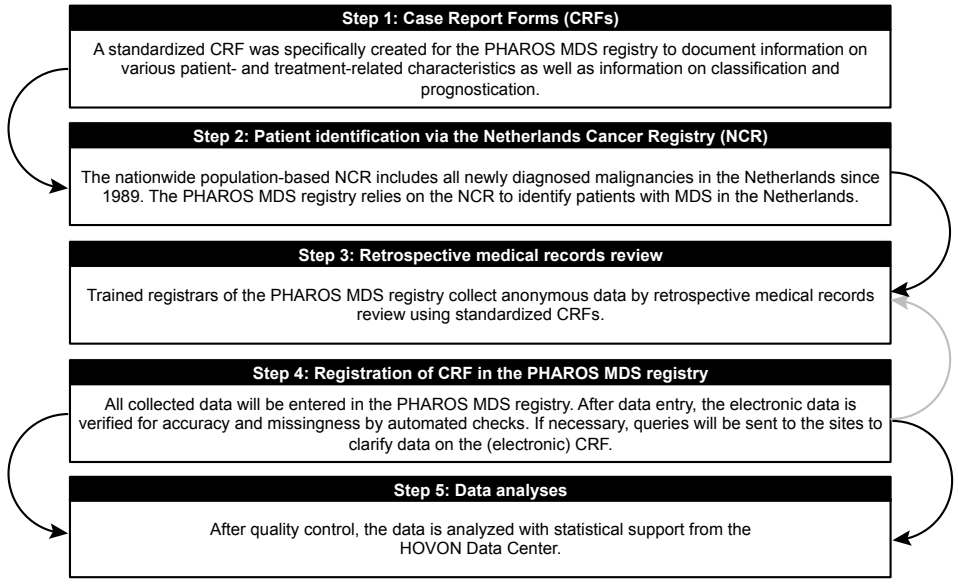
Established in 1989, the nationwide population-based Netherlands Cancer Registry (NCR), which is maintained and hosted by the Netherlands Comprehensive Cancer Organisation (IKNL), receives notification of all newly diagnosed malignancies in the Netherlands. The overall coverage of the NCR has been estimated to be at least 95%.[219] Since its establishment in 1989, the NCR covered a population of approximately 15 million inhabitants, which increased to almost 17 million in 2014. The most important notification sources of the NCR include the Nationwide Registry of Histopathology and Cytopathology (PALGA), to which all pathologic laboratories in the Netherlands report, and the Nationwide Hospital Discharge Registry (LMR). The NCR records an anonymized, minimal dataset for every newly diagnosed cancer patient. That data is collected by trained registration clerks of the NCR through retrospective medical records review according to standardized procedures set by the NCR, which follows the guidelines of the WHO and the International Association of Cancer Registries (IACR). The minimal dataset of the NCR includes information on dates of birth and diagnosis, sex, morphology, topography and stage of the tumor, and broad categories of primary treatment. Vital statistics of patients (alive, dead or emigration) are retrieved by annually linking the NCR to the Nationwide Population Registries Network, which holds vital statics of all Dutch residents; therefore, follow-up is accurate and complete.

The Dutch population-based PHAROS registry

Population-based cancer registries, such as the NCR, are primarily intended to provide statistics on incidence and mortality of cancers in the general population.[13] Such registries can also be used to complement RCTs to support clinical decision-making, provided that the registry has a good coverage of the defined population (i.e. at least 95%), include relevant parameters, and has an accurate follow-up.[220,221] Although the NCR meets with these criteria, the minimal dataset of the NCR is not sufficient enough to address more specific questions regarding the delivery of care to cancer patients, which necessitates additional, more detailed data. For instance, in the setting of hematological malignancies, guideline

adherence cannot be thoroughly evaluated as specific disease-related quality indicators are lacking in the NCR (e.g. IPSS for MDS is not recorded). Also, it is not possible with the minimal dataset of the NCR to assess the effectiveness of specific novel therapeutic agents in routine clinical practice (e.g. azacitidine for higher-risk MDS). Therefore, for selected hematological malignancies, the Dutch **P**opulation-based **HA**ematological **R**egistry for **O**bservational **S**tudies (PHAROS) was established to document additional, more detailed data on various patient-, disease- and treatment-related characteristics next to the minimal dataset of the NCR. The PHAROS registry is a joint initiative of HOVON, the institute of Medical Technology Assessment at the Erasmus University Rotterdam and IKNL. Currently, the PHAROS registry includes the following hematological malignancies: non-Hodgkin lymphoma (NHL), multiple myeloma (MM), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), MDS, CMML and primary myelofibrosis (pMF). The study design of the PHAROS MDS registry is shown in Figure 1. In brief, the PHAROS MDS registry includes adult (≥18 years) patients diagnosed with MDS and CMML in the Netherlands between January, 2008 and December, 2011 according to the disease definitions set by the WHO classification. While the NCR entirely covers the Netherlands, the PHAROS MDS registry essentially covers the west part of the Netherlands with 6.3 million inhabitants (approximately 40% of the Dutch population). As for the other above-mentioned indications, the PHAROS registry also covers at least the south part of the Netherlands (i.e. the area of North Brabant and North Limburg).

Figure 1. Study design of the PHAROS MDS registry. Figure adapted from Dinmohamed *et al*.[222]



The Dutch medical claims-based Information System

Cancer registries are considered the gold standard for cancer surveillance in the general population. Medical claims-based databases may complement cancer registry data, especially when particular malignancies, such as MDS, might be underreported in cancer registries.

All residents of the Netherlands are obliged by law to take out a healthcare insurance policy for the standard package that covers in- and outpatient care, general practitioner and medical specialist services, medication, durable medical equipment, home health care and hospice care. All policyholders are charged with a flat-rate premium for the standard healthcare insurance package. Hence, healthcare insurance companies are restricted to charge higher premiums, for example to the sick or the elderly. Treatment decisions in the Netherlands are therefore not based on financial considerations but on patient- and disease-related factors.

Dutch medical claims contain information on all activities that were performed to diagnose and treat a patient. In the Netherlands, medical claims are referred to as '*Diagnose Behandeling Combinatie*' (DBC) packages. The nationwide Dutch DBC Information System maintains all DBCs that has been sent by hospitals for billing purposes. In addition, they can provide anonymized data on DBC medical claims for scientific research.

SCOPE AND OUTLINE OF THE THESIS

Most of our knowledge on MDS, CMML and AML come from clinical studies. However, most patients included in clinical studies may not be entirely representative of the general patient population. Moreover, clinical studies are not suitable for the study of patients in the general population; therefore, other research platforms are needed to address the general patient population. The studies described in this thesis are divided into three parts and centered on the use of various Dutch population-based registries to assess different epidemiologic aspects of MDS, CMML and AML at the population level in the Netherlands.

The first part of the thesis (**chapters 2, 3 and 4**) utilizes the nationwide population-based NCR to provide insight into the burden of MDS, CMML and AML in the Netherlands. More specifically, we assess nationwide trends in incidence, treatment and survival among newly diagnosed patients with MDS (**chapter 2**), CMML (**chapter 3**) and AML (**chapter 4**). In addition, we assess patterns of clinical trial participation among patients with AML (**chapter 4**).

The second part centers on the question whether MDS and CMML may be underreported in the NCR (**chapter 5**). To address this question, the Dutch medical claims-based DBC Information System is used to assess the incidence of MDS and CMML in the Netherlands. Findings from that study are directly compared with incidence data from the NCR.

The third and final part of the thesis (**chapters 6 and 7**) centers around the use of the PHAROS MDS registry to extend on particular findings described in chapters 2 and 3, which are based on the minimal dataset of the NCR. In **chapter 6**, we studied various baseline characteristics, and patterns of diagnostic procedures and disease management among patients with MDS and CMML in routine clinical practice in the Netherlands. The aim of that study is to characterize the population in terms of baseline clinical and disease-related features, as well as to investigate whether patients are diagnosed and treated according to the national recommendations. In **chapter 7**, we set out the investigate the effectiveness of azacitidine compared with intensive chemotherapy and BSC only for the treatment of transplant-ineligible patients with higher-risk MDS in the Netherlands. The efficacy of azacitidine was clearly demonstrated in the phase 3 AZA-001 trial, which led to its approval for use in routine clinical practice. However, after its approval, it is unknown what the effectiveness of azacitidine is for patients treated in Dutch routine clinical practice.

Finally, in **chapter 8**, important findings of the thesis are summarized and discussed. In addition, future perspectives are discussed as well.

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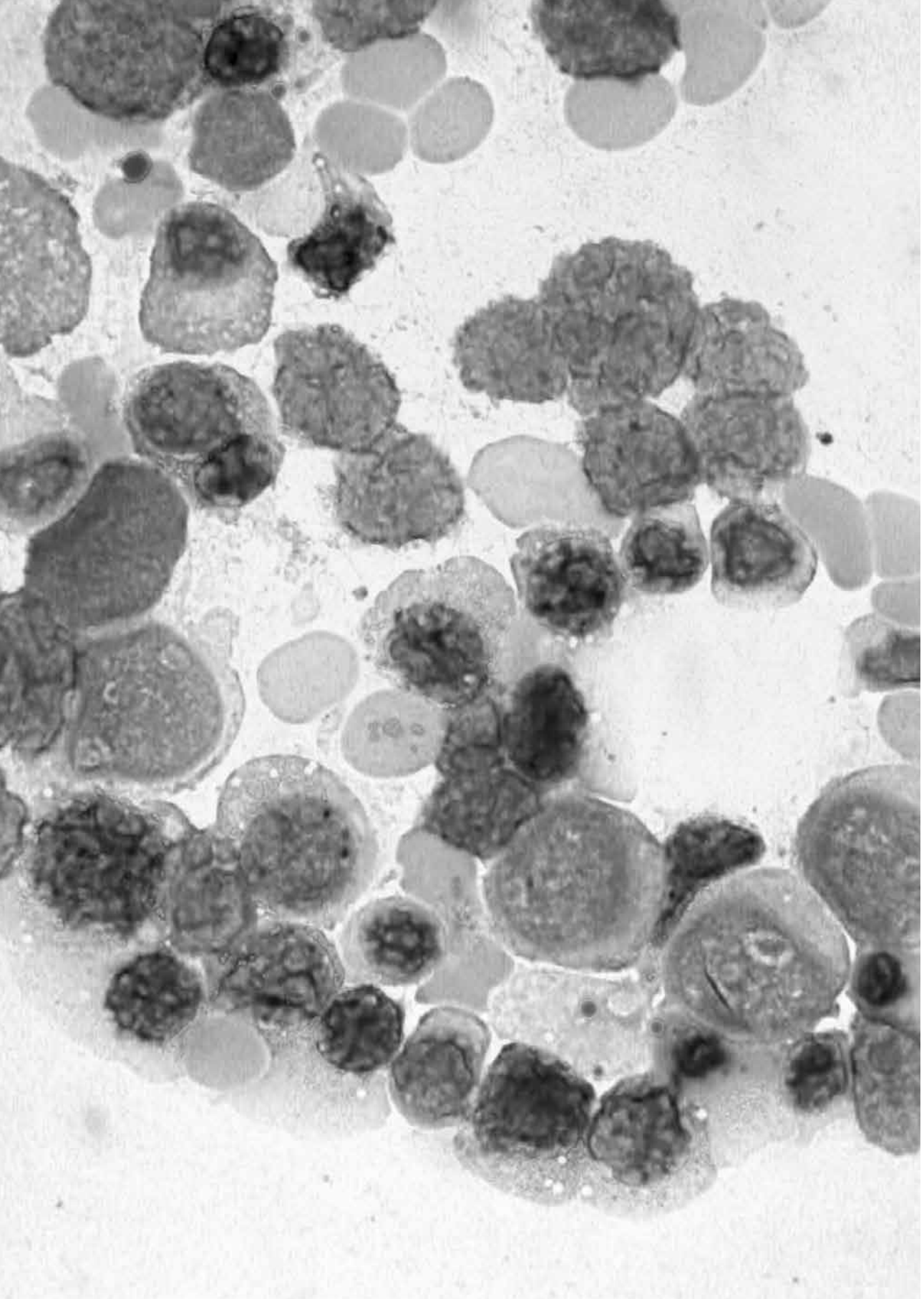

Trends in incidence, initial treatment and survival of myelodysplastic syndromes: a population-based study of 5,144 patients diagnosed in the Netherlands from 2001 to 2010

2

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ABSTRACT

Background

Studies with long-term follow-up of patients with myelodysplastic syndromes (MDS) based on data from nationwide population-based cancer registries are lacking. We conducted a nationwide population-based study to assess trends in incidence, initial treatment and survival in MDS patients diagnosed in the Netherlands from 2001-2010.

Methods

We identified 5,144 MDS patients (median age, 74 years) from the Netherlands Cancer Registry (NCR). The NCR only includes MDS cases that were confirmed by bone marrow examinations. Information regarding initial treatment decisions was available in the NCR.

Results

The age-standardized incidence rate of MDS was 2.3/100,000 in 2001-2005 and 2.8/100,000 in 2006-2010. The incidence increased with older age, with the highest incidence among those aged ≥80 years (32.1/100,000 in 2006-2010). Forty-nine percent of all MDS cases were unspecified. Of all patients, 89% receive no treatment or only supportive care and 8% were started on intensive therapy as initial treatment. Survival did not improve over time. Five-year relative survival was 53%, 58%, 48%, 38% and 18% in patients with refractory anemia (RA), RA with ringed sideroblasts, 5q- syndrome, refractory cytopenia with multilineage dysplasia, and RA with excess blasts, respectively.

Conclusion

The incidence of MDS increased over time due to improved notification and better disease awareness, and has stabilized since 2007. The classification of MDS seems challenging as almost half of the pathologically confirmed cases were unspecified. The lack of improvement in survival might be explained by the limited availability of therapeutic agents. Therefore, ameliorated management and new treatment options are warranted.

INTRODUCTION

The myelodysplastic syndromes (MDS) constitute a heterogeneous group of clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis and an increased risk of leukemic transformation.[1] At the beginning of the new millennium, the World Health Organization (WHO) classified MDS as malignant myeloid neoplasms,[2,3] and consequently MDS became reportable malignancies to population-based cancer registries as of 2001. The age-standardized incidence rate (ASR) of MDS is currently 2.0 to 3.4 per 100,000 in Western countries and the incidence increases sharply with older age.[4-8] Life expectancy of patients with MDS is variable and is dependent on the MDS subtype, and several clinical and prognostic parameters.[9-13] Treatment decisions also rely on clinical and prognostic parameters.[14-16]

Recent clinical studies have reported favorable outcomes in patients with MDS after treatment with immunomodulatory agents (e.g. lenalidomide[17]) or hypomethylating agents (i.e. azacitidine[18] and decitabine[19]). Survival data derived from clinical trials can be biased, however, because of patient selection (e.g. exclusion of elderly patients with comorbidities);[20] therefore, inference about the general patient population might not be made. The availability of nationwide population-based studies with long-term follow-up on incidence and survival in an unselected MDS population are lacking. In the few reported population-based studies on incidence and survival in MDS, the period of patient inclusion was short and the follow-up period was limited.[4-6,21] Furthermore, population-based studies regarding treatment decision in the entire MDS population have not been reported previously.

We have performed a nationwide population-based study in more than 5,000 newly diagnosed patients with MDS in the Netherlands from 2001 to 2010 reported to the Netherlands Cancer Registry (NCR). The aim of this study was to assess trends in incidence, initial treatment and survival among these MDS patients.

PATIENTS AND METHODS

The Netherlands Cancer Registry

Established in 1989, the population-based nationwide NCR is maintained and hosted by the Comprehensive Cancer Centres. The NCR is based on notifications of all newly diagnosed malignancies in the Netherlands by the automated nationwide archive of histopathology and cytopathology (PALGA), to which all pathological laboratories report. The NCR also receive notifications from the national registry of hospital discharges and various hematology departments. Information on date of birth, sex, date of diagnosis, morphology, and initial treatment decision is routinely collected by trained registrars from the medical records. The registrars register the diagnosis that is given by the treating physician. Initial treatment is recorded in four categories by the NCR, namely no therapy or only supportive care, chemotherapy, chemotherapy followed by a stem cell transplantation (SCT), and other therapy.

Diagnostic criteria and study population

MDS was included in the NCR as of January 1, 2001 when the International Classification of Diseases for Oncology Third Edition (ICD-O-3) was implemented for case ascertainment.[2] Notification of MDS is possibly incomplete in the first years after implementation of the ICD-O-3 seeing that implementation of the new WHO classification into clinical practice and notification sources of the NCR will have been delayed. Cases of MDS classified as non-malignant after 2000 will not have been notified to the NCR.

The NCR exclusively includes MDS cases that were confirmed by bone marrow examinations. All MDS subtypes according to the ICD-O-3 morphology codes are included in the NCR, namely refractory anemia (RA; 9980), RA with ringed sideroblasts (RARS; 9982), RA with excess blasts (RAEB; 9983), refractory cytopenia with multilineage dysplasia (RCMD; 9985), MDS with isolated deletion 5q (5q- syndrome; 9986) and MDS not otherwise specified (MDS NOS; 9989). The ICD-O-3 is developed by the WHO and is in accordance with the disease definitions according to the third edition of the WHO classification of hematological malignancies.[3]

All patients diagnosed with MDS between 2001 and 2010 were identified from the NCR. Patients were observed from date of diagnosis to date of death, date of emigration or end of follow-up (i.e. February 1, 2012). Death dates were retrieved from the nationwide population registries network, which holds vital statistics of all Dutch residents.

Statistical analysis

ASRs of MDS were calculated per 100,000 person-years for the entire study period (2001-2010), two calendar periods (2001-2005 and 2006-2010) and year of diagnosis, using the annual mid-year population size as obtained from Statistics Netherlands. Incidence rates were age-standardized to the European standard population. ASRs were also calculated according to sex and MDS subtype. Besides, we calculated the age-specific incidence for five age categories.

Relative survival rates (RSRs) with 95% confidence intervals (CIs) were calculated as a measure of disease-specific survival. The RSR is defined as the ratio between the observed survival in the group of patients and the expected survival of a comparable group from the general population. Expected survival was calculated using the Hakulinen method from Dutch population life tables according to age, sex and period.[22] RSRs were calculated for the entire study period, the two abovementioned calendar periods and year of diagnosis. Furthermore, RSRs were calculated by MDS subtype, age category and sex. Median Kaplan-Meier overall survival (OS) was calculated during the entire study period for the latter three characteristics. Patients aged <18 years at diagnosis (*n*=53) and patients diagnosed at autopsy (*n*=3) were excluded from the survival analysis. All statistical analyses were performed with STATA version 12.0 (College Station, TX).

RESULTS

We identified a total of 5,144 newly diagnosed patients with MDS during the study period (Table 1). Their median age at diagnosis was 74 years and 86% were 60 years of age or older at diagnosis. Regarding the subtypes of MDS, 486 (9%) were classified as RA, 583 (11%) RARS, 82 (2%) the 5q- syndrome, 524 (10%) RCMD, 966 (19%) RAEB, while 2,503 (49%) were unspecified (Table 1). The proportion of unspecified MDS decreased from 60% in 2001 to 36% in 2010 (data not shown). The annually reported number of patients diagnosed with MDS increased throughout the study period; however, the annual ASR stabilized at 2.8 per 100,000 since 2007 (Fig. 1). Incidence increased clearly with older age, with the highest incidence among those aged 80 years or older (Table 1). Men had a higher overall ASR than women (3.7 and 1.9 per 100,000 in 2006-2010, respectively), which was mainly attributed to the higher incidence of MDS in the over 70-year old men compared with the equivalent female group (Table 1).

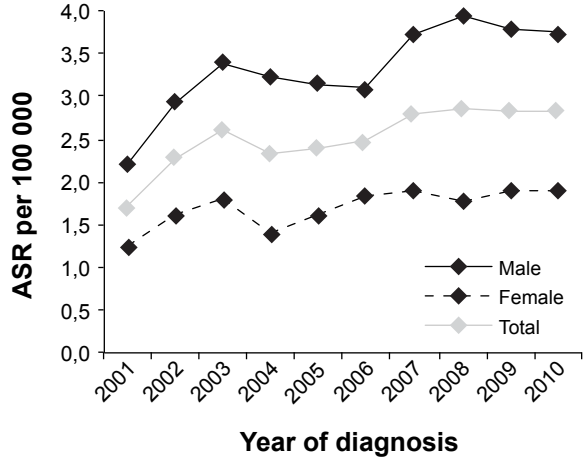
Of all patients, 4,562 (89%) did not receive treatment or only received supportive care, 348 (7%) received chemotherapy and 74 (1%) received chemotherapy + SCT as initial treatment (Table 2). The use of chemotherapy and chemotherapy + SCT decreased with increasing age group. Chemotherapy and chemotherapy + SCT were more frequently applied in patients with RAEB than in patients with other MDS subtypes. Treatment decisions for the two calendar periods were similar (data not shown).

Relative survival did not improve over time (Fig. 2). RSRs by MDS subtypes are shown in Figure 3A. Five-year RSRs were 53% for RA, 58% for RARS, 48% for the 5q- syndrome, 38% for RCMD, 18% for RAEB, and 39% for unspecified MDS (Fig. 3A). The 1-, 3-, 5- and 10-year RSRs by age categories are shown in Figure 3B. Age at diagnosis was an important predictor for relative survival as RSRs decreased in parallel with older age. Sex did not influence RSRs (Supplementary Fig. S1). Median Kaplan-Meier OS by MDS subtype, age at diagnosis and sex are shown in Table 3.

Table 1. Age-standardized incidence rates of MDS in the Netherlands by MDS subtype and demographic characteristics, 2001-2010.

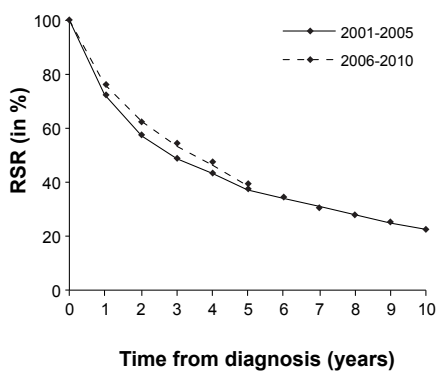
	Calendar period								
	2001-2005			2006-2010			Total		
Characteristics	**No.**	**(%)**	**ASR[a]**	**No.**	**(%)**	**ASR[a]**	**No.**	**(%)**	**ASR[a]**
Total No. of patients	2,163		2.26	2,981		2.76	5,144		2.51
MDS subtype									
RA	234	(10.8)	0.24	252	(8.5)	0.24	486	(9.4)	0.24
RARS	230	(10.6)	0.24	353	(11.8)	0.32	583	(11.3)	0.28
5q- syndrome	14	(0.6)	0.02	68	(2.3)	0.06	82	(1.6)	0.04
RCMD	90	(4.2)	0.09	434	(14.6)	0.40	524	(10.2)	0.24
RAEB	363	(16.8)	0.40	603	(20.2)	0.58	966	(18.8)	0.49
MDS NOS	1,232	(57.0)	1.28	1,271	(42.6)	1.16	2,503	(48.7)	1.22
Sex									
Male	1,277	(59.0)	2.97	1,798	(60.3)	3.66	3,075	(59.8)	3.32
Female	886	(41.0)	1.54	1,183	(39.7)	1.86	2,069	(40.2)	1.70
Age, years (both sexes)									
Median (p10-p90)	74 (54-85)			75 (57-85)			74 (55-85)		
<50	142	(6.6)	0.25	155	(5.2)	0.26	297	(5.8)	0.26
50-59	197	(9.1)	1.79	229	(7.7)	2.01	426	(8.3)	1.90
60-69	426	(19.7)	5.86	616	(20.7)	7.19	1,042	(20.3)	6.53
70-79	820	(37.9)	16.48	1,092	(36.6)	20.47	1,912	(37.2)	18.48
≥80	578	(26.7)	24.95	889	(29.8)	32.13	1,467	(28.5)	28.54
Age, years (male)									
Median (p10-p90)	73 (54-84)			74 (58-84)			74 (56-84)		
<50	74	(5.8)	0.26	77	(4.3)	0.26	151	(4.9)	0.26
50-59	115	(9.0)	2.08	146	(8.1)	2.55	261	(8.5)	2.32
60-69	270	(21.1)	7.54	398	(22.1)	9.31	668	(21.7)	8.42
70-79	501	(39.2)	22.31	701	(39.0)	28.24	1,202	(39.1)	25.27
≥80	317	(24.8)	36.27	476	(26.5)	44.61	793	(25.8)	40.44
Age, years (female)									
Median (p10-p90)	74 (53-86)			76 (56-86)			75 (55-86)		
<50	68	(7.7)	0.23	78	(6.6)	0.27	146	(7.1)	0.25
50-59	82	(9.3)	1.51	83	(7.0)	1.46	165	(8.0)	1.48
60-69	156	(17.6)	4.18	218	(18.4)	5.07	374	(18.1)	4.63
70-79	319	(36.0)	10.65	391	(33.1)	12.71	710	(34.3)	11.68
≥80	261	(29.5)	13.62	413	(34.9)	19.65	674	(32.6)	16.64

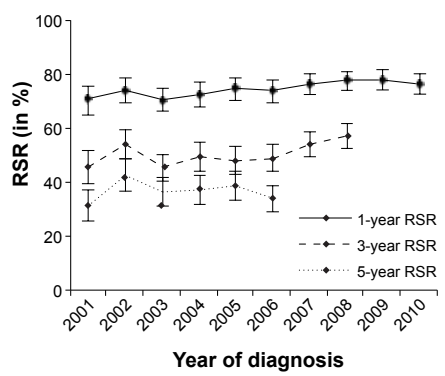
Abbreviations: ASR, age-standardized incidence rate; MDS, myelodysplastic syndromes; RA, refractory anemia; RARS, RA with ringed sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia; RAEB, RA with excess blasts; MDS NOS, MDS not otherwise specified. [a] presented per 100,000 person-years.



Sex	ASR by year of diagnosis									
	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Male	2.20	2.92	3.38	3.23	3.14	3.12	3.71	3.95	3.78	3.74
Female	1.25	1.63	1.81	1.41	1.62	1.84	1.91	1.76	1.91	1.90
Total	1.72	2.27	2.60	2.32	2.38	2.48	2.81	2.85	2.84	2.82

Figure 1. Annual age-standardized rates (ASRs) of MDS in the Netherlands from 2001 to 2010 by sex.





Calendar period	RSR (in %) with 95% CI			
	1-year	3-year	5-year	10-year
2001-2005	73 (71 to 75)	49 (46 to 51)	37 (35 to 40)	22 (20 to 26)
2006-2010	77 (75 to 78)	53 (51 to 55)	38 (35 to 42)	

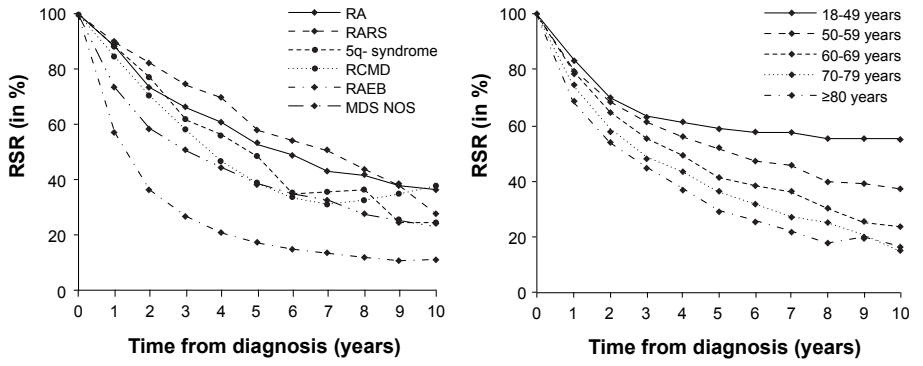
RSR	RSR (in %) by year of diagnosis									
	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
1-year	71	74	71	73	75	74	76	78	78	76
3-year	46	54	45	49	48	49	54	57		
5-year	31	42	36	37	39	34				

Figure 2. Relative survival rates (RSRs) among patients diagnosed with MDS in the Netherlands from 2001 to 2010 by (A) calendar period of diagnosis and (B) year of diagnosis. Vertical bars denote 95% confidence intervals (CIs).

Table 2 Initial treatment of MDS patients in the Netherlands by MDS subtype and age at diagnosis, 2001-2010.

	Age at diagnosis						Total	
	<65		65-79		≥80			
Initial treatment	**No.**	**(%)**	**No.**	**(%)**	**No.**	**(%)**	**No.**	**(%)**
Total No. of patients, all MDS subtypes	1,148		2,529		1,467		5,144	
No therapy or only supportive care	874	(76)	2,283	(90)	1,405	(96)	4,562	(89)
Chemotherapy	139	(12)	179	(7)	30	(2)	348	(7)
Stem-cell transplantation	68	(6)	6	(0)	0		74	(1)
Other therapy	23	(2)	45	(2)	28	(2)	96	(2)
Unknown	44	(4)	16	(1)	4	(0)	64	(1)
Total No. of patients, RA	113		250		123		486	
No therapy or only supportive care	97	(86)	237	(95)	120	(98)	454	(93)
Chemotherapy	3	(3)	6	(2)	1	(1)	10	(2)
Stem-cell transplantation	4	(4)	0		0		4	(1)
Other therapy	2	(2)	5	(2)	2	(2)	9	(2)
Unknown	7	(6)	2	(1)	0	(0)	9	(2)
Total No. of patients, RARS	105		298		180		583	
No therapy or only supportive care	101	(96)	285	(96)	175	(97)	561	(96)
Chemotherapy	1	(1)	7	(2)	3	(2)	11	(2)
Stem-cell transplantation	0		0		0		0	
Other therapy	2	(2)	4	(1)	1	(1)	7	(1)
Unknown	1	(1)	2	(1)	1	(1)	4	(1)
Total No. of patients, 5q- syndrome	25		34		23		82	
No therapy or only supportive care	19	(76)	23	(68)	22	(96)	64	(78)
Chemotherapy	6	(24)	8	(24)	1	(4)	15	(18)
Stem-cell transplantation	0		0		0		0	
Other therapy	0		2	(6)	0		2	(2)
Unknown	0		1	(3)	0		1	(1)
Total No. of patients, RCMD	114		247		163		524	
No therapy or only supportive care	97	(85)	226	(91)	161	(99)	484	(92)
Chemotherapy	8	(7)	11	(4)	0		19	(4)
Stem-cell transplantation	5	(4)	1	(0)	0		6	(1)
Other therapy	3	(3)	9	(4)	2	(1)	14	(3)
Unknown	1	(1)	0		0	0	1	(0)
Total No. of patients, RAEB	277		482		207		966	
No therapy or only supportive care	136	(49)	375	(78)	186	(90)	697	(72)
Chemotherapy	79	(29)	92	(19)	11	(5)	182	(19)
Stem-cell transplantation	44	(16)	4	(1)	0		48	(5)
Other therapy	2	(1)	9	(2)	10	(5)	21	(2)
Unknown	16	(6)	2	(0)	0		18	(2)
Total No. of patients, MDS NOS	514		1,218		771		2,503	
No therapy or only supportive care	424	(82)	1,137	(93)	741	(96)	2,302	(92)
Chemotherapy	42	(8)	55	(5)	14	(2)	111	(4)
Stem-cell transplantation	15	(3)	1	(0)	0		16	(1)
Other therapy	14	(3)	16	(1)	13	(2)	43	(2)
Unknown	19	(4)	9	(1)	3	(0)	31	(1)

Abbreviations: RA, refractory anemia; RARS, RA with ringed sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia; RAEB, RA with excess blasts; MDS NOS, MDS not otherwise specified.



MDS subtype	RSR (in %) with 95% CI			
	1-year	3-year	5-year	10-year
RA	88 (85 to 91)	66 (60 to 71)	53 (46 to 59)	37 (28 to 46)
RARS	90 (86 to 93)	74 (69 to 79)	58 (51 to 64)	28 (17 to 41)
Del(5q)	88 (78 to 95)	61 (48 to 73)	48 (33 to 63)	25 (7 to 52)
RCMD	85 (81 to 88)	58 (52 to 63)	38 (31 to 46)	38 (28 to 49)
RAEB	57 (54 to 60)	27 (24 to 31)	18 (15 to 21)	11 (8 to 15)
MDS NOS	73 (71 to 75)	50 (48 to 53)	39 (36 to 41)	23 (19 to 27)

Age at diagnosis (years)	RSR (in %) with 95% CI			
	1-year	3-year	5-year	10-year
18-49	84 (79 to 88)	63 (56 to 69)	59 (52 to 65)	55 (47 to 62)
50-59	81 (76 to 84)	61 (56 to 66)	52 (46 to 57)	37 (30 to 45)
60-69	80 (77 to 82)	56 (52 to 59)	41 (37 to 45)	24 (19 to 29)
70-79	74 (72 to 76)	49 (46 to 52)	36 (33 to 39)	15 (10 to 21)
≥80	68 (66 to 71)	45 (41 to 48)	29 (25 to 34)	17 (8 to 31)

Figure 3. Relative survival among patients diagnosed with MDS in the Netherlands from 2001 to 2010 by (A) MDS subtype and (B) age at diagnosis. *Abbreviations*: RSR, relative survival rate; and CI, confidence interval.

Table 3 Median overall survival of patients diagnosed with MDS in the Netherlands by MDS subtype, age at diagnosis and sex, 2001-2010.

Characteristics	No. patients	Median OS, months (95% CI)
Total	5,088	28 (27-30)
MDS subtype		
RA	485	50 (40-55)
RARS	583	55 (49-59)
5q- syndrome	81	44 (29-65)
RCMD	521	36 (31-42)
RAEB	955	14 (13-16)
MDS NOS	2,463	27 (24-30)
Age, years		
18-49	243	NR
50-59	426	61 (46-74)
60-69	1,040	40 (36-46)
70-79	1,910	27 (25-30)
≥80	1,469	19 (17-21)
Sex		
Male	3,039	27 (25-28)
Female	2,049	31 (29-35)

Abbreviations: OS, overall survival; MDS, myelodysplastic syndromes; RA, refractory anemia; RARS, RA with ringed sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia; RAEB, RA with excess blasts; MDS NOS, MDS not otherwise specified; NR, not reached.

DISCUSSION

To our knowledge, this is the first nationwide population-based study reporting on incidence, initial treatment and survival among newly diagnosed patients with MDS during a 10-year period since MDS were formally classified as malignant neoplasms in 2001.

The data are consistent with a rise in the annually reported number of MDS patients throughout the study period. However, the annual ASR has stabilized since 2007; the initial rise is presumably due to better case ascertainment and classification as well as improved disease awareness, rather than changes in etiologic factors. The overall ASR for our cohort does not deviate much from those recently reported in other Western countries (Table 4).

Table 4 A selected overview of recent incidence rates of MDS in Western countries. Incidence rates were quoted in original references.

Study	Country or region	Study period	Incidence[a]			Age-specific incidence[a]				
			Total	M	F	<50	50-59	60-69	70-79	≥80
This study	The Netherlands	2001-2005	2.3	3.0	1.5	0.3	1.8	5.9	16.5	25.0
		2006-2010	2.8	3.8	1.9	0.3	2.0	7.2	20.5	32.1
Rollison *et al.*[5]	USAb	2001-2003	3.3	4.4	2.5	-	2.0	7.1	20.1	35.5
Ma *et al.*[4]	USAc	2001-2003	3.4	4.5	2.7	-	4.1	26.8		
Smith *et al.*[7]	Yorkshire & Humber (UK)	2004-2009	2.5	4.0	1.5	-	-	-	-	-
Neukirchen *et al.*[8]	Düsseldorf (Germany)	1996-2005	2.5	-	-	-	-	-	-	-
Sant *et al.*[6]	Europed	2000-2002	2.0	-	-	-	-	-	-	-

[a], presented per 100,000 person-years;
[b], based on data from the North American Association of Cancer Registries (NAACR);
[c], based on data from the Surveillance, Epidemiology, and End Results (SEER) program;
[d], based on data from 13 European cancer registries with stable incidence rates for MDS over the study period.
-, no information available on incidence for the corresponding category.
Abbreviations: M, male; F, female; USA, United States of America; UK, United Kingdom.

Despite the detailed WHO classification of MDS,[3,23] 49% of all pathologically confirmed MDS cases in our study were unspecified. We assume that the group of patients for whom the MDS subtype was not specified is a heterogeneous group including both patients with lower- and higher-risk MDS. Interestingly, the proportion of specified cases increased over time, especially RCMD. This finding might support the notion that physicians and pathologists became increasingly aware of the WHO classification of MDS. Nevertheless, still 36% of all MDS cases were unspecified in 2010. This all goes to say that proper classification of MDS at diagnosis leaves much to be desired. Therefore, recommendations from the European LeukemiaNET on diagnosis in adult MDS have recently been adapted in Dutch guidelines to optimize diagnostic procedures in MDS.[24]

The initial treatment of MDS patients was conservative throughout the study period. Patients could have received treatment after disease progression; however, data on subsequent treatment choices were not available for our cohort. Also, concomitant comorbidities might affect therapeutic decision making in MDS. Studies on comorbidities in an unselected MDS population are scarce. A recent single-center cohort study of MDS patients suggested an association of comorbidities with outcome, independent of known risk factors.[25] Data on comorbidities in our cohort were only available in a minor subset of patients. At least one comorbidity was recognized in more than half of the patients in that particular subset (data not shown, Eindhoven Cancer Registry).

Relative survival of MDS patients did not improve over the study period, which underlines the increasing need to ameliorate treatment strategies of MDS. Survival was better in patients with RA or RARS than in patients with more advanced MDS as shown in other studies as well.[4,9,21,26,27] Excess mortality in patients with RA and RARS is mainly caused by infections, progressive bone marrow failure or bleeding complications.[28] The management of RA and RARS in the Netherlands includes supportive care (e.g. red blood cell transfusions or administration of hematopoietic growth factors) and intensive therapy for selected patients as recommended by internatioal guidelines.[14-16] Supportive care in MDS aims to correct cytopenias and to minimize symptoms, so as to improve quality of life.[29]

The WHO classification of MDS recognizes the 5q- syndrome and RCMD as distinct MDS entities, seeing their different clinical and morphological phenotypes.[3] The prognosis is thought to be more favorable for patients with the 5q- syndrome.[27,30] In our study, however, 5-year relative survival was only 48%. Survival could perhaps be improved by administration of lenalidomide.[31] So far, however, lenalidomide has not yet been registered in the Netherlands for clinical use in MDS.

Consistent with the literature as well, RAEB was associated with the poorest survival of all MDS subtypes.[4,9,21] During the study period, treatment used in higher-risk MDS in the Netherlands included intensive therapy (i.e. acute myeloid leukemia (AML)-like chemotherapy and/or allogeneic SCT) for patients who are considered fit for these treatment modalities. Alternatively, azacitidine became available in the Netherlands since 2009 for patients with International Prognostic Scoring System intermediate-2 and high-risk MDS who are not considered fit for intensive therapy. It remains to be seen, though, whether the beneficial effect of azacitidine on survival will be apparent in an unselected subgroup of higher-risk MDS patients in the Netherlands. Additionally, decitabine showed similar efficacy as azacitidine;[19] however, decitabine is not registered in Europe for clinical use in MDS.

As previously reported as well,[4,5,21] survival decreased in parallel with older age. The poor prognosis in elderly patients might be explained by the concomitant comorbidities as well as the limited availably of treatment options for that particular patient group.

Sex, however, did not seem to influence relative survival; in contrast to other studies.[4,5]

The strength of our study is that we used a nationwide population-based cancer registry to identify newly diagnosed MDS patients. The use of a nationwide registry generalizes our findings to the entire MDS population. The NCR exclusively includes MDS cases that were confirmed by bone marrow examinations and according to the disease definitions of the WHO classification.[3,23] This classification was preceded by the French-American-British classification of MDS which also included the subtypes RAEB in transformation and chronic myelomonocytic leukemia.[32] These have been merged with other categories in the WHO classification of hematological malignancies.[3]

Several limitations of our study should be addressed. Recently, two medical claims-based studies showed that MDS patients aged ≥65 years were underreported in population-based cancer registries in the US.[33,34] This may also hold true for the NCR. An important diagnostic procedure in MDS is the morphological evaluation of the bone marrow.[14-16,24,35] It may be the case that the diagnosis of MDS, especially in elderly patients, is solely based on the evaluation of the peripheral blood without performing a bone marrow examination. In these cases, a diagnosis of MDS would be questionable. In our study, however, we exclusively included MDS cases that were confirmed by bone marrow examinations; therefore we feel that our results are largely representative for the general MDS population. Secondly, no data were available regarding diagnostic procedures, prognostication, time to leukemic transformation and all treatment regimens for our cohort. Data from large population-based cancer registries on MDS progressing into AML are lacking. Therefore, the European Network of Cancer Registries (ENCR) recently made recommendations how to register a hematological malignancy that transforms into a new morphological entity.[36] The NCR will implement the abovementioned recommendation as population-based cancer registry data on progression of MDS to AML will be of interest. Treatment strategies rely on the patients' risk stratification, which typically considers several prognostic parameters such as the number[9] and depth[13] of cytopenias or cytogenetics.[9,10,13] However, we cannot assess whether treatment decisions in our cohort followed the international recommendations for the management of MDS. To address aspects in routine clinical practice regarding diagnostic procedures and treatment decisions in MDS, population-based registries including this information are needed. An extended population-based registry of the NCR for hematological malignancies (i.e. the **P**opulation-based **HA**ematological **R**egistry for **O**bservational Studies—the PHAROS registry) was established in 2009, which collects information on clinical data such as diagnostic procedures (e.g. cytogenetics), prognostication (e.g. IPSS and revised IPSS) and all treatment regimens. In the future, data from the PHAROS MDS registry will provide more insight into diagnostic procedures and treatment decisions in routine clinical practice.

In conclusion, we noted that the incidence of MDS increased over time due to improved notification to the NCR and has stabilized since 2007. Morphological assessment of MDS according to the WHO classification seems challenging as almost half of the pathologically confirmed cases were unspecified. Nevertheless, the proportion of specified cases increased over time, which was presumably due to increased awareness of the WHO classification of MDS. The lack of improvement in patient survival might be explained by the limited availability of therapeutic agents. Therefore, it is necessary to improve current treatment strategies and to develop new treatment options in MDS.

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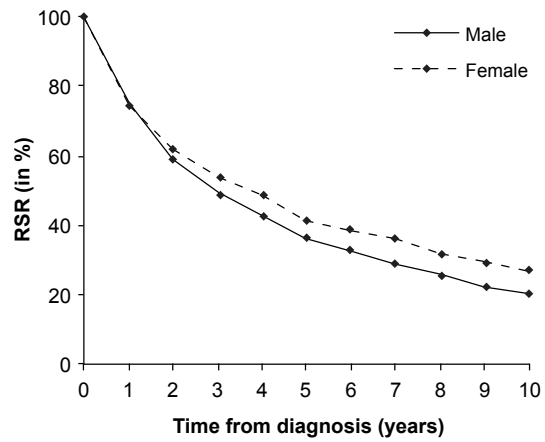
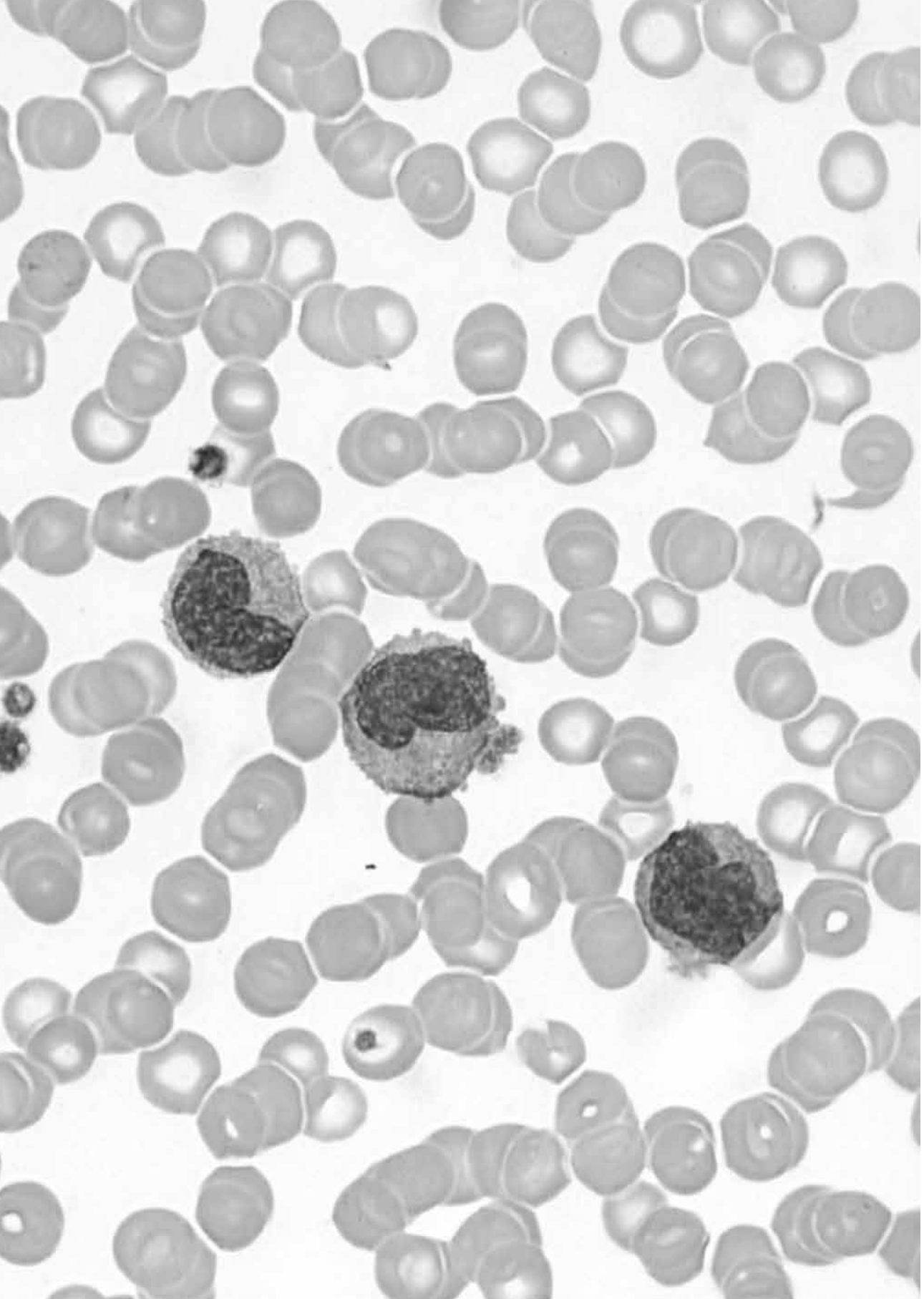


	RSR (in %) with 95% CI			
Sex	1-year	3-year	5-year	10-year
Male	75 (73 to 77)	49 (47 to 52)	36 (34 to 39)	20 (16 to 25)
Female	75 (73 to 77)	54 (51 to 56)	42 (39 to 44)	27 (22 to 31)

Supplemental Figure 1. Relative survival among patients diagnosed with MDS in the Netherlands from 2001 to 2010 by sex. *Abbreviations*: RSR, relative survival rate; and CI, confidence interval.



Trends in incidence, primary treatment and survial in chronic myelomonocytic leukaemia: a popultion-based study of 1359 patients diagnosed in the Netherlands from 1989 to 2012

3

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Chronic myelomonocytic leukaemia (CMML) is a rare, heterogeneous haematological malignancy characterized by features of both myelodysplastic syndromes (MDS) and myeloproliferative neoplasms.[1] Most,[2,3] but not all,[4] outcome data in CMML arrive from the few available clinical trials where CMML was grouped with MDS and only included a small number of CMML patients, which were not reported separately. In this regard, population-based studies can provide data complementary to findings from clinical trials by specifically addressing an unselected CMML population. So far, the few available population-based studies in CMML have limitations including, small sample sizes, short study and follow-up length, or registries that only partially cover the country.[5,6]

Given the paucity of clinical trials and large population-based studies in CMML, we conducted a large, nationwide population-based study to assess trends in incidence, primary treatment and survival among more than 1300 CMML patients diagnosed in the Netherlands.

We selected all over 18-year-old CMML patients diagnosed between 1989-2012 (*n* = 1359; median age, 75 years; age range, 22-95 years; 62% males; Table 1) with follow-up through February, 2014, from the nationwide population-based Netherlands Cancer Registry (NCR). The NCR, which is maintained and hosted by the Comprehensive Cancer Centre the Netherlands, has a nationwide coverage of >95% of all malignancies in the Netherlands since 1989. Despite changes in classification, CMML has a separate morphology code in all editions of the International Classification of Diseases for Oncology (ICD-O) and could therefore be identified in the NCR throughout the entire study period (ICD-O-1, 9893/3; ICD-O-2, 9868/3 and ICD-O-3, 9945/3). The ICD-O does not have separate codes for CMML-1 and 2. The NCR ascertains CMML cases that were confirmed by the physician through histology and/or cytology. Data on the dates of birth, diagnosis and last known vital status (alive, death or emigration), sex, hospital of diagnosis and primary treatment (no therapy or only supportive care, chemotherapy and chemotherapy + stem cell transplantation) were available for individual patients.

Based on changing classifications and age-adapted treatment approaches, we divided patients into three periods (1989-2000, 2001-2006 and 2007-2012) and four age groups (18-59, 60-69, 70-79 and ≥80 years), unless otherwise stated. Relative survival rates (RSRs) were calculated according to the classic cohort approach as a measure of disease-specific survival. The RSR is the ratio of the observed survival of patients to the expected survival in the general population for the same age, sex and period.

The annual age-standardized incidence rate (ASR) of CMML increased until 2007 and thereafter remained stable at around 0,4/100 000 (Fig S1A). The proportion of patients diagnosed in individuals ≥70 years was 72% (Table 1). Seventy-eight percent of the patients were diagnosed in non-university hospitals.

Of all patients, 975 (72%), 365 (27%) and 19 (1%) received no therapy or only supportive care, chemotherapy and chemotherapy + stem cell transplantation (CT+SCT)

as primary treatment, respectively. The primary treatment was similar during the three periods studied (Fig S2). Chemotherapy was given to 50%, 36%, 25% and 17% of the patients in the four age groups, respectively. CT+SCT was only applied in 13 (11%) of 119 and 6 (2%) of 273 patients aged 18-59 and 60-69 years, respectively (Fig S2).

Relative survival (RS) did not improve over time as 5-year RSRs were 16%, 20% and 20% in the three periods, respectively (Figure 1A). RS was poor among all age groups, reflected in an overall 5-year RSR of 21%, 23%, 20% and 12% for the four age groups, respectively (Figure 1B). Although limited by small numbers (*n* = 19), the overall 5-year RSR was 29% (95% confidence interval: 10%-52%) for patients undergoing CT+SCT as primary treatment.

In our large population-based study, the ASR of CMML initially increased, likely as a result of improved case ascertainment, augmented disease awareness and better classification, rather than changes in etiologic factors. The diagnosis of CMML can be challenging as it primarily relies on morphological assessment of blood and bone marrow smears, along with cytogenetic evaluation, in patients with persistent monocytosis. Despite the well-known diagnostic challenges in CMML, the overall ASR in our cohort is comparable with recent reports from other Western countries.[5,6]

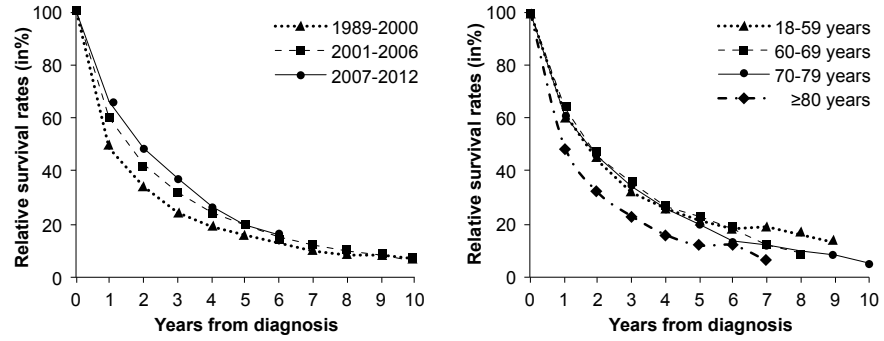
Our results show that RS was poor in all age groups and did not improve over the past two decades, which warrants the need to improve outcomes for CMML patients. The finding that survival is generally poor in CMML is congruent with other smaller series;[4-8] however, it has not been demonstrated before in a large population-based study. Treatment options for CMML patients are limited and the vast majority are not eligible for curative treatment (i.e. an allogeneic SCT) due to advanced age at diagnosis. Treatment approaches for transplant-ineligible patients include hypomethylating agents, hydroxyurea, erythropoietic stimulating agents and supportive care.[1] However, most of these approaches are often extrapolated from experience and knowledge gained in MDS as data for their specific use in CMML are scarce. Therefore, although CMML is rare, clinical trials should specifically evaluate therapeutic interventions in this disease in order to establish evidence-based treatment guidelines. Several CMML-specific risk-stratification models were recently proposed, including traditional parameters in combination with either cytogenetics[9] or *ASXL1* mutation status,[10] which are able to segregate patients into risk groups with distinct outcomes. These prognostic models can also help to guide risk-adapted treatment and to design specific clinical CMML trials.

The strengths of our study include the use of a nationwide population-based cohort, large number of patients and long-term study period. Limitations include the lack of specific clinical information, such as the bone marrow blast count, cytogenetics, and subsequent treatment choices. Despite these limitations, cancer registries are pivotal for determining trends in incidence and survival of malignant disorders in the general population.

Table 1. Demographic characteristics of patients diagnosed with chronic myelomonocytic leukaemia in the Netherlands from 1989 to 2012.

Characteristics	Period of diagnosis									Total (1989-2012)		
	1989-2000			2001-2006			2007-2012					
	No.	(%)	ASR*	No.	(%)	ASR*	No.	(%)	ASR*	No.	(%)	ASR*
Total No. of patients	467		0,23	373		0,31	519		0,38	1359		0,30
Sex												
Male	286	(61)	0,33	231	(62)	0,43	332	(64)	0,53	849	(62)	0,42
Female	181	(39)	0,14	142	(38)	0,19	187	(36)	0,23	510	(38)	0,18
Age, years												
Median	74			75			76			75		
18-49	20	(4)	0,02	10	(3)	0,01	7	(1)	0,01	37	(3)	0,02
50-59	25	(5)	0,12	25	(7)	0,19	32	(6)	0,23	82	(6)	0,17
60-69	95	(20)	0,61	78	(21)	0,88	100	(19)	0,92	273	(20)	0,77
70-79	195	(42)	1,86	157	(42)	2,65	214	(41)	3,31	566	(42)	2,49
≥80	132	(28)	2,83	103	(28)	3,37	166	(32)	4,88	401	(30)	3,62
Hospital type												
Non-university	372	(80)	-	289	(77)	-	405	(78)	-	1066	(78)	-
University	95	(20)	-	84	(23)	-	114	(22)	-	293	(22)	-

ASR, age-standardized incidence rate.
*Age-standardized to the European standard population and presented per 100 000 person-years.



Calendar period	Relative survival rate (in%) with 95% CI			
	1-year	3-year	5-year	10-year
1989-2000	49 (44-54)	24 (20-28)	16 (12-20)	7 (4-10)
2001-2006	60 (54-65)	32 (28-38)	20 (15-25)	6 (3-11)
2007-2012	66 (62-70)	37 (32-41)	20 (15-25)	-

Age group	Relative survival rate (in%) with 95% CI			
	1-year	3-year	5-year	10-year
18-59	62 (52-70)	32 (23-40)	21 (13-29)	-
60-69	64 (57-69)	36 (30-42)	23 (18-29)	-
70-79	61 (57-65)	34 (29-38)	20 (16-24)	5 (2-9)
≥80	50 (45-56)	23 (18-29	12 (7-18)	-

Figure 1. Relative survival rates (RSRs) of over 18-year-old patients with chronic myelomonocytic (CMML) leukaemia in the Netherlands, 1989-2012. (**A**) Relative survival of patients with CMML according to period of diagnosis and (**B**) relative survival of patients with CMML during the entire study period of 1989-2012 according to age at diagnosis.

In summary, CMML is a rare, aggressive malignancy with limited treatment options available. As a result, RS remained poor and essentially unchanged over the past two decades in younger and older CMML patients. Therefore, CMML-specific prognostic scoring systems should be applied in the diagnostic work-up to assess prognosis and to provide risk-adapted therapy, and assist in designing specific clinical trials for CMML patients in order to improve their survival.

ACKNOWLEDGEMENTS

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SUPPORTING FIGURE LEGENDS

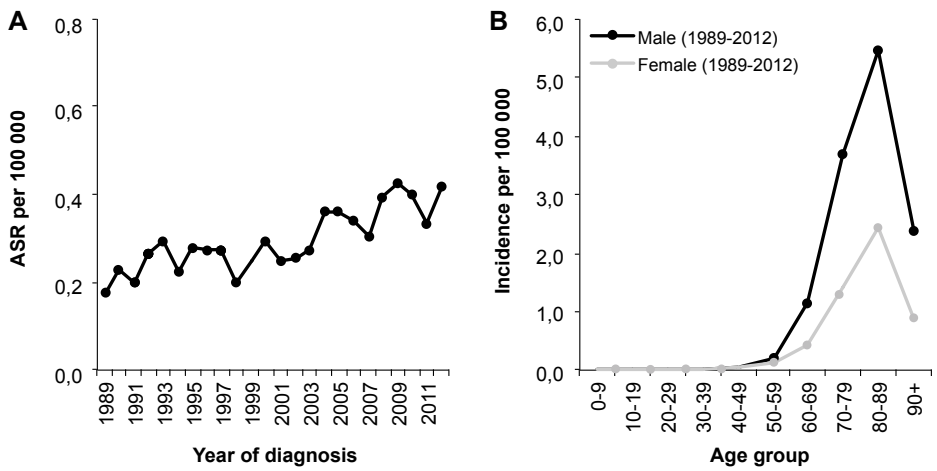
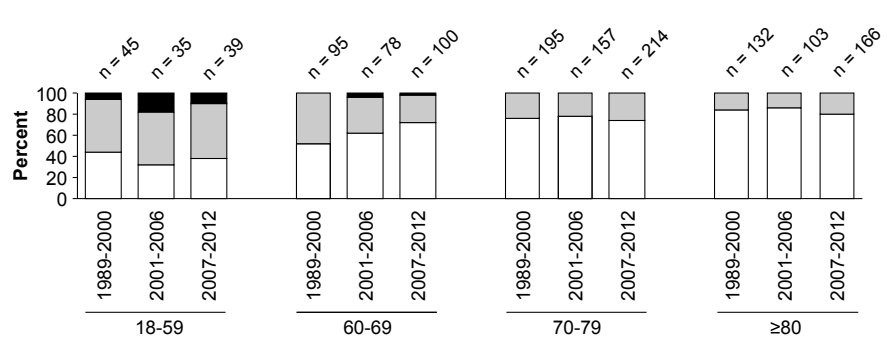
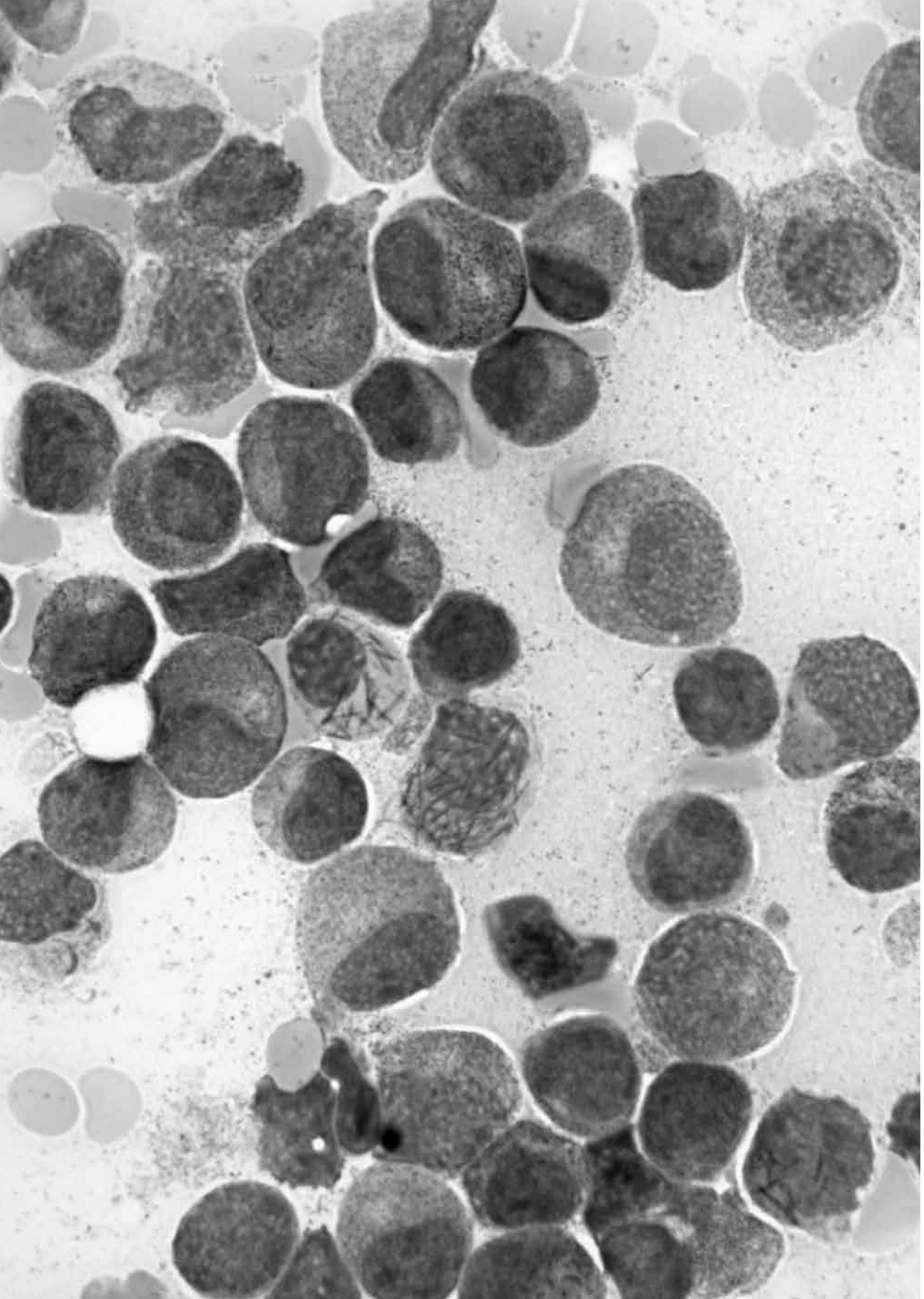


Fig S1. (A) Annual age-standardized incidence rates (ASRs) and (B) age-specific incidence rates of chronic myelomonocytic leukaemia in the Netherlands, 1989-2012.



Treatment	Column percentage											
□ NT/SC*	44	31	38	53	62	71	75	77	74	84	86	81
▒ CT	49	51	51	47	35	26	25	23	26	16	14	19
■ CT+SCT	7	17	10	-	4	3	-	-	-	-	-	-

Fig S2. Primary treatment of over 18-year-old patients with chronic myelomonocytic leukaemia in the Netherlands from 1989 to 2012 by age at diagnosis and period of diagnosis. The table presents the proportion of patients receiving a particular treatment within a specific calendar period and age group. Discrimination between non-intensive (e.g. hydroxyurea and azacitidine) and intensive chemotherapy was only possible with data from two regional registries that approximately covers 20% of the Dutch population. Data from those registries revealed that among patients aged 18-69 years treated with chemotherapy, 20 (54%) of 37 patients received intensive vs. 46% non-intensive chemotherapy. NT/SC indicates no therapy or only supportive care; CT, chemotherapy and SCT, stem cell transplantation. *Includes 5 patients with unspecified therapy.



Treatment, trial participation and survival in adult acute myeloid leukemia: a population-based study in the Netherlands, 1989-2012

4

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ABSTRACT

Large, comprehensive population-based studies in acute myeloid leukemia (AML) are scarce. We conducted a nationwide population-based study on treatment, trial participation and survival among all adult patients diagnosed with AML (N=12,032) and acute promyelocytic leukemia (APL; N=585) in the Netherlands between 1989-2012. Patients were categorized into four periods and four age groups (18-40, 41-60, 61-70, and >70 years). The application of allogeneic stem cell transplantation increased over time among AML patients up to age 70. For APL patients, the use of chemotherapy increased across all age groups. When a clinical trial was open for accrual in the Netherlands, the inclusion rates were 68%, 57%, 30% and 12% for AML patients in the four age groups, respectively (data for APL unavailable). Relative survival improved over time among AML (up to age 70) and APL patients. In the period 2007-2012, 5-year relative survival rates were 54%, 38%, 14% and 2% for AML patients and 84%, 75%, 54% and 37% for APL patients in the four age groups, respectively. As survival remained poor for older AML patients over the last two decades, clinical trials, and active participation in those trials, are warranted that explore innovative treatment strategies for this elderly population.

INTRODUCTION

Acute myeloid leukemia (AML) is a clonal hematopoietic progenitor cell disorder, which affects individuals at any age with a continuously progressive increase with older age.[1] AML has an overall age-standardized incidence rate of 3 to 4 per 100,000 in Western countries and the median age at diagnosis is around 65-70 years.[2,3] The disease is very heterogeneous with regard to patient- and disease-related characteristics as well as treatment response and outcome.[1] AML is usually rapidly fatal if specific treatment is not promptly initiated after diagnosis.[4]

The treatment strategy with a curative intent in AML generally consists of two consecutive phases: intensive remission induction chemotherapy and consolidation therapy.[5] This treatment strategy, however, may be poorly tolerated by older or medically unfit patients in which case treatment-related mortality may be high.[6] Generally, treatment strategies are adjusted according to pre-treatment (e.g. patient- and disease-related characteristics) and post-treatment factors (e.g. response after induction therapy) that allow for identification of patients who would likely tolerate and benefit from a specific type of treatment strategy.[5] The therapeutic armamentarium against AML has remained relatively stable over the past decades. However, substantial progress has been made towards optimizing existing treatment strategies rather than involvement of novel therapeutic agents,[7] except the introduction of all-*trans* retinoic acid (ATRA) and arsenic trioxide for the treatment of acute promyelocytic leukemia (APL),[8] which is an entity of AML with specific molecular, biologic and clinical characteristics.[9] Much of the remarkable progress can be credited to improvements in supportive care,[10,11] advances in understanding the dose-response relationships and dose intensification of induction chemotherapy,[12,13] the application of allogeneic stem cell transplantation to a greater number of patients,[14] and developments in better risk-stratification models and risk-adapted treatment approaches.[15]

Randomized controlled clinical trials are essential to evaluate new interventions and to establish evidence-based clinical practice guidelines. Recently published clinical trials show that 40% to 50% of younger[13,16-18] and around 10% of older patients with AML can be cured.[12,19,20] However, the study populations of clinical trials are not representative of the general patient population. Indeed, evidence from the few available population-based studies revealed that patients with AML from the general population have comparatively unfavorable features (e.g. advanced age and secondary AML) and worse outcome compared with patients enrolled in clinical trials.[21-26] Thus, findings from clinical trials are based on selected patient populations and therefore their value cannot be generalized to the non-studied population. Population-based studies can complement clinical trial studies and lend additional data informing clinical decision-making.[27] Furthermore,

nationwide population-based studies that address the question of accrual patterns of patients with AML in clinical trials have yet to be published.

Here we report the results of a comprehensive, nationwide population-based study among more than 12,000 adult patients diagnosed with AML in the Netherlands from 1989 to 2012 reported to the nationwide population-based Netherlands Cancer Registry (NCR). The aim of the study was to assess trends in treatment, trial participation and survival across the entire adult AML population during this 24-year period.

METHODS

Registry and study population

The NCR, which is maintained and hosted by the Netherlands Comprehensive Cancer Organisation, has an overall coverage of more than 95% of all malignancies in the Netherlands since 1989.[28] The NCR is primarily based on notifications by the Nationwide Archive of Histo- and Cytopathology (PALGA), to which all pathological laboratories in the Netherlands report, followed by the National Registry of Hospital Discharges (LMR). The NCR collects information on dates of birth and diagnosis, sex, disease topography and morphology, primary treatment and hospital of diagnosis and treatment. The date of last known vital status (alive, dead or emigration) was retrieved by linking the NCR to the nationwide population registries network, which holds vital statistics of all Dutch residents.

The NCR codes disease topography and morphology according to the International Classification of Diseases for Oncology (ICD-O). The first edition of the ICD-O was used for case ascertainment until 1992, the second edition (ICD-O-2) from 1993 to 2000, the third edition (ICD-O-3) from 2001 to 2011, and an updated ICD-O-3 from 2012 onwards. The ICD-O-2 is based on the disease definitions of the French-American-British classification of AML,[29] while the ICD-O-3 and its update are based on the third[30] and fourth[31] edition of the World Health Organization (WHO) classification of hematological malignancies, respectively.

Patients diagnosed with AML between 1989-2012 were selected from the NCR using ICD-O morphology codes as listed in Supplementary Table S1. Before the release of the third edition of the WHO classification of hematological malignancies[30] and the ICD-O-3[32] in 2001, myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN) were considered non-malignant hematologic diseases. Therefore, the progression from MDS or MPN to AML was included in the NCR as a first incident case of AML before 2001, while as of 2001, MDS and MPN were included in the registry as an incident case and the progression to AML (that is, secondary AML) was not standardly registered since 2001, but only in the calendar period 2003-2009. To investigate the effect of secondary AML on survival, we excluded these cases from the primary AML sample in the calendar period 2003-2009. This analysis revealed that the effect of secondary AML on survival was negligible (see Online Supplementary Results). Therefore, in order to maintain a relatively consistent cohort, we excluded these cases of secondary AML from our study population since 2001, as they were not consistently recorded since 2001. Collectively, any bias related to the exclusion of secondary AML after 2001 may only have marginally biased our results. All patients were observed from the date of diagnosis to death, emigration or end of follow-up (February 1st, 2014), whichever occurred first. We categorized AML cases into two groups: AML without APL and APL. Detailed clinical information, such as prognostic factors and remission rates, were not available in the NCR.

Treatment

Treatment after diagnosis is recorded by the NCR and was registered as supportive care only, chemotherapy or chemotherapy followed by a hematopoietic stem cell transplantation (SCT). To obtain information on the type of SCT (autologous [auto] or allogeneic [allo] SCT), anonymous data including this information were provided by the SCT Working Party of the Dutch-Belgian Cooperative Trial Group for Hemato-Oncology (HOVON), and subsequently linked to the NCR. Details about the linking methodology, results of the linkage, and treatment definitions are provided in the online Supplementary Material.

Trial participation

Since 1985, the HOVON performs clinical AML trials in the Netherlands. Parallel to the HOVON, the European Organization for Research and Treatment of Cancer (EORTC) performs clinical AML trials in particular institutions in the Netherlands. Data regarding trial participation are unavailable in the NCR. Therefore, anonymous data of patients with AML included in clinical trials were provided by the HOVON and EORTC. Details regarding the linking methodology, results of the linkage and analyses of trial participation are described in the online Supplementary Material.

Statistical analyses

Relative survival rates (RSRs) with 95% confidence intervals (CIs) were calculated as a measure of disease-specific survival according to the cohort methodology. Relative survival is the ratio of the observed survival of patients to the expected survival of a comparable cohort from the general population, which is sex, age and period matched.[33] Expected survival was calculated by the Hakulinen method from Dutch population life tables according to age, sex and calendar period.[34] We calculated RSRs up to 10 years

from diagnosis for four calendar periods (1989-1994, 1995-2000, 2001-2006 and 2007-2012) and four age groups (18-40, 41-60, 61-70 and >70 years). To assess actuarial (overall) survival (OS) according to intervention by calendar period, the Kaplan Meier method was used. To analyze the probability of early death, a logistic regression analysis was performed with early death as the outcome. Early death is defined as death within 30 days from diagnosis. The probability of early death was calculated and expressed as odds ratios with 95% CIs. The analysis included the following independent categorical variables: sex, age at diagnosis, calendar period of diagnosis and hospital of diagnosis. The independent variables were assessed in a univariate manner. Only variables with a *P* value of less than 0.20 in univariate analysis were included in the multivariate analysis. A *P* value less than 0.05 was considered statistically significant. Patients age <18 years at diagnosis (n=615) and patients first diagnosed at autopsy (n=51) were excluded from the treatment and survival analyses. All statistical analyses were performed with STATA Statistical Software Release 13.1 (College Station, TX).

RESULTS

Demographic characteristics

A total of 12615 patients with AML (median age, 66 years) and 617 patients with APL (median age, 52 years) were diagnosed in the Netherlands between 1989 and 2012. Of all patients with AML and APL, 4% and 3% were diagnosed in patients below the age of 18 years, respectively. Characteristics and age-specific incidence rates of all patients are shown in Table 1 and Supplementary Figure S1, respectively.

The overall age-standardized incidence rate (ASR) of AML remained nearly constant over time (3.0 cases per 100 000; Table 1). A slight increase was observed after the year 2000 due to the revised blast threshold for the diagnosis of AML from 30% to 20% blasts in the bone marrow.[30] The age-specific incidence of AML rises sharply with older age (Supplementary Figure S1a). There is a consistent male predominance throughout the study period (Table 1), which relates to the higher incidence in the over 60-year-old men compared with the equivalent female group (Supplementary Figure S1a).

Patients with APL account for 4.7% of all AML cases and the average annual ASR is 0.15 cases per 100 000 in both sexes (Table 1). There is a female predominance in the period 1989-2000; however, this was the reverse in the period 2001-2012.

Treatment

Information on treatment of adult patients with AML and APL according to age at diagnosis and calendar period of diagnosis is shown in Figure 1a and 1b, respectively. The application of allo-SCT for AML increased over time among patients less than 70 years of age and the increase was most pronounced among patients 41-60 years of age (Figure 1a), increasing from 8% to 46%. Allo-SCTs were gradually introduced in the treatment of patients 61-70 years of age only during the early 2000s. There were no large regional differences in the application of allo-SCTs during the periods studied (data not shown). Details on region definition are provided in the online Supplementary Material. Allo-SCTs were more frequently performed than auto-SCTs over the study period (Figure 1a), with auto-SCT being applied in approximately 10% of patients and allo-SCT in 50% of patients. Of all allo-SCTs and auto-SCTs, 95% and 96% were performed during first complete remission and 5% and 4% during other disease phases, respectively. Although it was not possible to distinguish between intensive and palliative chemotherapy because of this information was not standardly registered across the system, sample data from two regional registries, covering one fifth of the Dutch population, revealed that for AML patients aged 18-40, 41-60, 61-70 and >70 years, 2%, 3%, 9%, and 39% received palliative chemotherapy which compares with values of 98%, 97%, 91%, and 61% for intensive chemotherapy, respectively. The vast majority of patients older than 70 years primarily received supportive care only throughout the entire study period (Figure 1a).

Table 1. Characteristics of patients diagnosed with AML and APL in the Netherlands, 1989-2012

Disease type	Characteristics	Calendar period 1989-1994 No.	(%)	1995-2000 No.	(%)	2001-2006 No.	(%)	2007-2012 No.	(%)	Total No.	(%)
AML	**Total No. of patients**	2599		2983		3365		3668		12615	
	Male/female ratio (%)	55/45		54/46		54/46		54/46		54/65	
	Age, years										
	Median	65		65		66		68		66	
	<18	137	(5)	137	(5)	171	(5)	138	(4)	583	(5)
	18-40	305	(12)	335	(11)	300	(9)	278	(8)	1218	(10)
	41-60	613	(24)	699	(23)	829	(25)	817	(22)	2958	(23)
	61-70	607	(23)	662	(22)	706	(21)	846	(23)	2821	(22)
	>70	937	(36)	1150	(39)	1359	(40)	1589	(43)	5035	(40)
	ASR per 100 000[a]										
	Total	2.80		2.95		3.10		3.03		2.97	
	Male	3.40		3.45		3.61		3.51		3.49	
	Female	2.21		2.45		2.59		2.55		2.45	
	Hospital type[b]										
	Non-university	1396	(54)	1544	(52)	1716	(51)	1873	(51)	6529	(52)
	University	1203	(46)	1439	(48)	1649	(49)	1795	(49)	6086	(48)
APL	**Total No. of patients**	108		140		177		192		617	
	Male/female ratio (%)	40/60		40/60		52/48		53/47		47/53	
	Age, years										
	Median	49		53		50		53		52	
	<18	10	(9)	7	(5)	9	(5)	6	(3)	32	(5)
	18-40	34	(31)	36	(26)	47	(27)	37	(19)	154	(25)
	41-60	25	(23)	46	(33)	65	(37)	82	(43)	218	(35)
	61-70	16	(15)	18	(13)	23	(13)	31	(16)	88	(14)
	>70	23	(21)	33	(24)	33	(19)	36	(19)	125	(20)
	ASR per 100 000[a]										
	Total	0.11		0.14		0.17		0.17		0.15	
	Male	0.10		0.12		0.18		0.19		0.15	
	Female	0.13		0.15		0.16		0.16		0.15	
	Hospital type[b]										
	Non-university	45	(42)	52	(37)	59	(33)	71	(37)	227	(37)
	University	63	(58)	88	(63)	118	(67)	121	(63)	390	(63)

Abbreviations: ASR, age-standardized incidence rate; AML: acute myeloid leukemia; APL: acute promyelocytic leukemia. [a] Incidence rates are age-standardized to the European standard population. [b] Patients referred from a non-university hospital to a university hospital were categorized as university hospital.

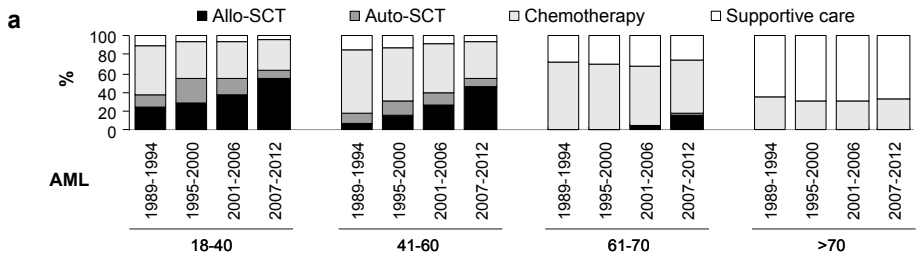


Figure 1. Treatment of adult patients with (**a**) AML and (**b**) APL in the Netherlands by age at diagnosis and calendar period of diagnosis, 1989-2012. The table presents the proportion of patients receiving a particular treatment within a specific calendar period and age group. The absolute number of patients within a specific calendar period and age group is shown in Table 1.

The use of chemotherapy for APL increased over time in all age groups (including patients >70 years of age) and this trend was most evident among patients 18-40 years of age (Figure 1b). The application of SCTs for APL decreased over time and has become very uncommon in the most recent calendar period.

Trial participation

All clinical AML trials in the Netherlands use intensive induction chemotherapy courses, followed by a particular consolidation therapy (that is, another course of intensive chemotherapy, auto-SCT or allo-SCT) within the trial. The decision to proceed to a particular consolidation therapy is based on the following patient and disease-related characteristics: age, type and severity of comorbidity, leukemia-related prognostic factors (that is, cytogenetics and molecular genetics), and donor availability.

Inclusion rates into clinical trials according to age are shown in Figure 2. The overall inclusion rate when a clinical trial was open for accrual in the Netherlands was 68%, 57%, 30%, and 12% for patients with AML 18-40, 41-60, 61-70, and >70 years of age, respectively. Ninety percent, 85%, 73% and 35% of the patients aged 18-40, 41-60, 61-70 and >70 years who had not been entered into a clinical trial and survived at least 30 days after diagnosis did receive intensive therapy (chemotherapy, auto-SCT and allo-SCT) outside the context of a clinical trial, respectively.

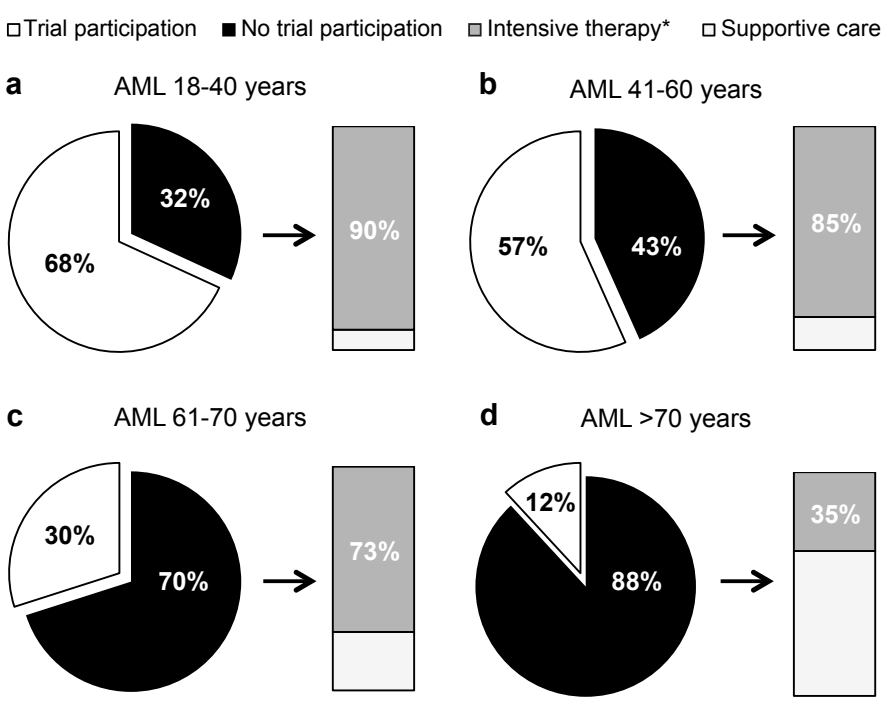


Figure 2. Trial participation of adult patients with AML in the Netherlands according to age at diagnosis. The pie chart depicts the proportion of trial participation among patients aged (**a**) 18-40 years, (**b**) 41-60 years, (**c**) 61-70 years and (**d**) >70 years. The bar plot depicts the treatment given to patients who did not entered into a clinical trial. *Intensive therapy includes chemotherapy, auto-SCT and allo-SCT.

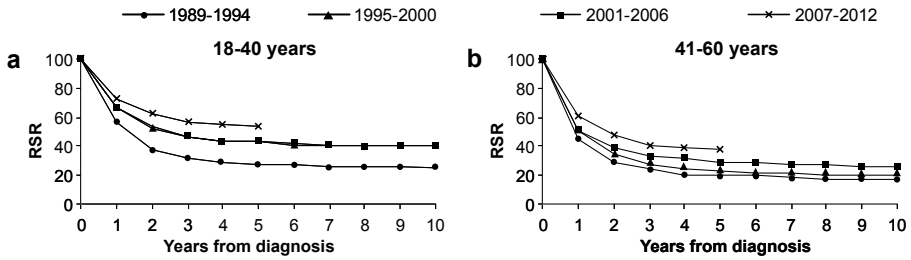
Survival

The overall 5-year RSRs increased from 12% (95% CI: 11%-14%) in 1989-1994 to 20% (95% CI: 18%-21%) in 2007-2012 among adult patients with AML and from 45% (95% CI: 35%-54%) in 1989-1994 to 66% (95% CI: 58%-74%) in 2007-2012 among adult patients with APL (Supplementary Figure S2). Large survival differences among the different regions were not noted during the study period (data not shown).

One- and 5-year RSRs only improved over time in patients with AML 70 years of age or younger (Figures 3a to c), although it was most pronounced among patients 18-40 and 41-60 years of age, especially in the most recent calendar period (Figures 3a and b). To investigate the possible contributions for the marked survival improvement among 18-60-year-olds (Figures 3a and b, and 4a), we estimated the OS for these patients according to treatment and calendar period of diagnosis. Five-year OS was the highest for recipients of an allo-SCT, namely 52% (95% CI: 47%-57%) in the most recent calendar period (Figure 4b). In that same calendar period, 5-year OS was 35% (95% CI: 30%-39%) for patients who received chemotherapy and auto-SCT (Figure 4c). Interestingly, the OS of the latter group increased over time; however, not as much as in the total group (Figure 4a), which also includes recipients of an allo-SCT. Survival among patients older than 70 years of age remained comparatively low throughout the calendar periods studied (Figure 3d).

Overall improvements in RSRs were more pronounced in APL than in AML. Baseline survival among patients with APL 60 years of age or younger was relatively high in the first calendar period under study (Figures 5a and b). One- and 5-year RSRs increased most notably among patients older than 60 years of age (Figures 5c and d).

The overall early death rate, i.e. death within 30 days from diagnosis, was 24% and 20% among patients with AML and APL, respectively. Early death rates of patients with AML and APL according to age and calendar period of diagnosis are shown in Supplementary Figure S3. The probability of early death only decreased for patients with AML diagnosed in the calendar period 2007-2012 compared with patients diagnosed in the calendar period 1989-1994 as shown in Supplementary Table S3 by multivariate logistics regression analysis (odds ratio, 0.79; 95% CI: 0.69-0.89; P<0.001). For patients with APL, the decrease in the probability of early death did not reach statistical significance.



RSR	Calendar period			
	1989-1994	1995-2000	2001-2006	2007-2012
	RSR (in %) with 95% CI			
1-year	57 (51-62)	67 (61-71)	66 (61-72)	72 (67-77)
5-year	28 (23-33)	43 (37-48)	43 (37-49)	54 (47-60)

RSR	Calendar period			
	1989-1994	1995-2000	2001-2006	2007-2012
	RSR (in %) with 95% CI			
1-year	45 (41-49)	50 (47-54)	51 (47-54)	60 (57-64)
5-year	20 (17-23)	23 (20-27)	29 (26-32)	38 (34-42)

RSR	Calendar period			
	1989-1994	1995-2000	2001-2006	2007-2012
	RSR (in %) with 95% CI			
1-year	32 (28-36)	32 (28-36)	32 (28-35)	42 (38-45)
5-year	5 (3-7)	7 (5-10)	9 (7-12)	14 (11-17)

RSR	Calendar period			
	1989-1994	1995-2000	2001-2006	2007-2012
	RSR (in %) with 95% CI			
1-year	11 (9-14)	11 (9-13)	14 (11-16)	15 (13-17)
5-year	1 (0-2)	2 (1-3)	2 (1-3)	2 (1-3)

Figure 3. Relative survival rates (RSRs) of adult patients diagnosed with AML in the Netherlands according to age at diagnosis and calendar period of diagnosis, 1989-2012. RSRs are shown according to the following age categories: (**a**) 18-40 years, (**b**) 41-60 years, (**c**) 61-70 years and (**d**) >70 years. The table presents the projected 1- and 5-year RSRs with 95% confidence intervals (CIs) according to age at diagnosis and calendar period of diagnosis.

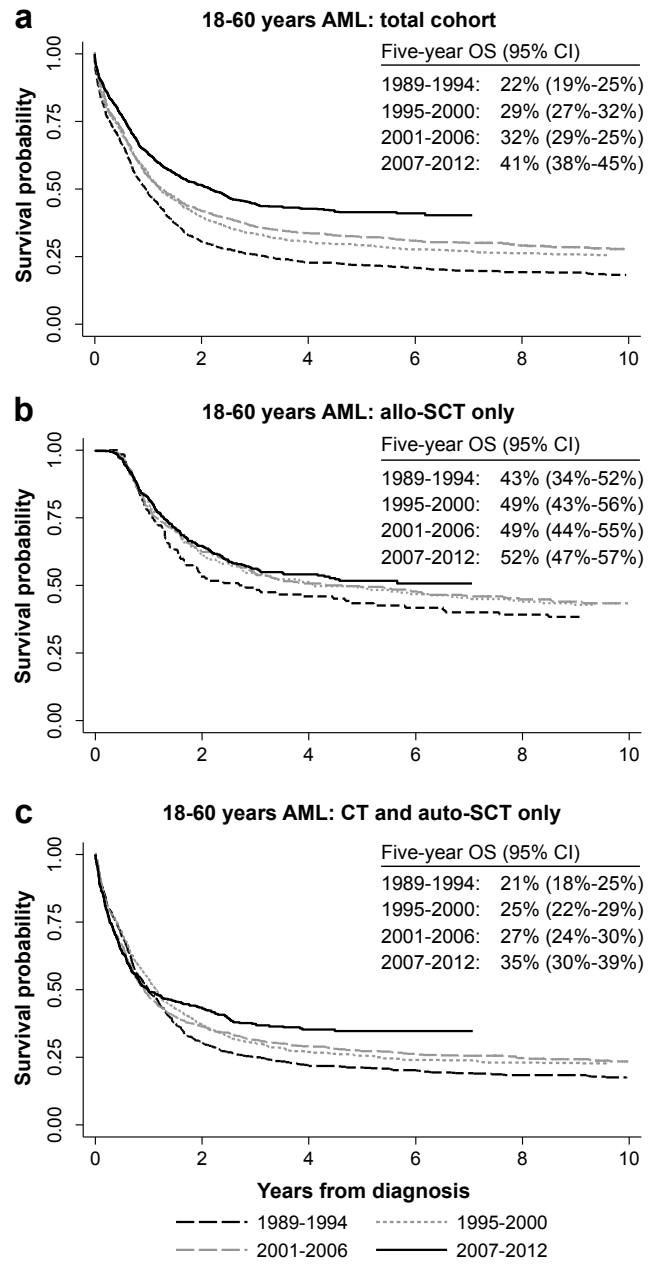
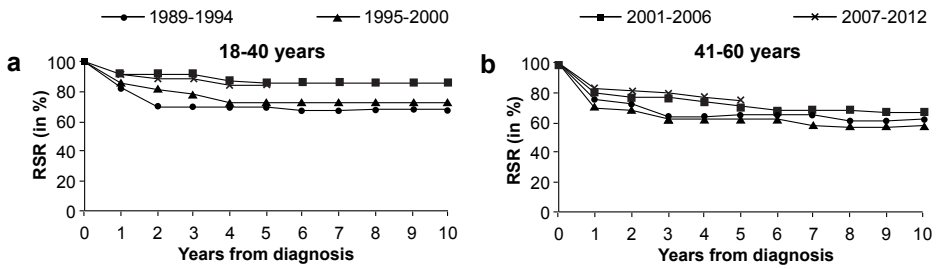


Figure 4. Overall survival (OS) of patients with AML 18-60 years of age according to treatment and calendar period of diagnosis, 1989-2012. Kaplan-Meier estimates of OS according to (a) all treatment choices (i.e. supportive care only, chemotherapy, allo-SCT and auto-SCT), (b) allo-SCT and (c) chemotherapy (CT) and auto-SCT.



RSR	Calendar period			
	1989-1994	1995-2000	2001-2006	2007-2012
	RSR (in %) with 95% CI			
1-year	82 (64-92)	86 (70-94)	92 (79-97)	92 (77-97)
5-year	70 (52-83)	73 (55-84)	85 (71-93)	84 (64-94)

RSR	Calendar period			
	1989-1994	1995-2000	2001-2006	2007-2012
	RSR (in %) with 95% CI			
1-year	76 (54-89)	70 (54-81)	80 (68-88)	83 (73-90)
5-year	64 (42-81)	62 (46-75)	71 (58-81)	75 (61-84)

RSR	Calendar period			
	1989-1994	1995-2000	2001-2006	2007-2012
	RSR (in %) with 95% CI			
1-year	25 (8-48)	40 (18-61)	62 (39-79)	69 (49-82)
5-year	0	36 (15-59)	38(18-58)	54 (33-73)

RSR	Calendar period			
	1989-1994	1995-2000	2001-2006	2007-2012
	RSR (in %) with 95% CI			
1-year	9 (2-26)	26 (12-43)	26 (12-43)	47 (29-62)
5-year	8 (1-33)	9 (2-26)	16 (5-33)	37 (19-58)

Figure 5. Relative survival rates (RSRs) of adult patients diagnosed with APL in the Netherlands according to age at diagnosis and calendar period of diagnosis, 1989-2012. RSRs are shown according to the following age categories: (a) 18-40 years, (b) 41-60 years, (c) 61-70 years and (d) >70 years. The table presents the 1- and 5-year RSRs with 95% confidence intervals (CIs) according to age at diagnosis and calendar period of diagnosis.

DISCUSSION

Most published population-based cancer registry studies in AML provide information on survival at the population level,[2,3,21,35-37] while only a few assessed the application of various treatments.[22,38,39] Further, long-term data are lacking on trial participation in an unselected AML population. Here we present comprehensive population-based assessments on treatment, trial participation and survival in an unselected AML population during a 24-year period.

The incidence of AML in the Netherlands appears comparable with data in reports from other Western countries.[2,3,21] Trends in APL incidence are in agreement with data from Sweden,[40] i.e. a lower incidence and a higher median age at diagnosis compared with other population-based reports,[3,41-43] and gender differences regarding age-specific incidence rates. These findings support previously noted differences in APL incidence between Northwestern Europe[40] and other areas such as Southern Europe[41] and Latin America.[42]

Some improvements in survival were observed in this study among patients with AML 70 years of age or younger, with the major improvement taking place during the most recent calendar period (2007-2012). The improvements in survival might be related to better post-remission therapies. In our population-based study, we showed that patients treated with intensive chemotherapy or auto-SCT as well as patients undergoing allo-SCT show improved outcome over time. These results compare well to those observed in Sweden, which also suggest improved outcome in regions with an increased application of intensive therapy.[44] The increased application of allo-SCT is in line with reports from SCT registries.[45,46] Several factors may have contributed to an overall increased application of allo-SCT. First, following the initial study by Slovak *et al*,[47] subsequent meta-analysis have shown that allo-SCT more strongly reduces relapse in patients in first complete remission as compared to alternative post-remission strategies.[16,48] Still, the indication for allo-SCT in first remission for specific prognostic subgroups (for example, intermediate-risk) is not yet clearly settled.[49] Secondly, the increased availability of alternative donors, leading to a possible donor for the majority of AML patients nowadays.[50] Third, the advent of reduced-intensity condition regimes and improved supportive care possibilities leading to a reduction of non-relapse mortality and a safer application of allo-SCT.[51]

It is notable that the survival among patients with AML older than 70 years of age did not improve since the early 1990, which was also observed in other population-based studies.[21,35-37] The majority of patients older than 70 years of age are often unsuitable candidates for intensive and potentially curative therapy due to comorbidities and poor performance status. However, a subset of patients 70-79 years of age may benefit from intensive chemotherapy compared with palliation alone as shown by population-based data from Sweden.[22] Therefore, it is important to identify elderly patients that are likely

to benefit from intensive therapy by using prognostic models, including comorbidity index scores and geriatric assessments, which aid in treatment decision-making.[5,6,52,53] For those patients deemed ineligible for intensive therapy, a subset might benefit from less intensive disease-modifying agents such as the hypomethylating agents azacitidine[54,55] and decitabine.[56]

Randomized controlled clinical trials are essential in order to assess new interventions and to establish evidence-based clinical practice guidelines. We show that around 40% of patients with AML up to 60 years of age were not included in clinical trials; however, around 90% of those patients received intensive treatment outside the setting of a clinical study. The accrual rates of patients with AML decreased rapidly above the age of 60 years, a phenomenon also observed in other cancer trials.[57] Based on findings from the few regional studies in AML, the most frequent reasons for non-inclusion were: advanced age, comorbidities and an antecedent malignancy, including a hematologic malignancy (e.g. myelodysplastic syndromes).[23-25] In the Netherlands, all residents are legally obliged to take out a Dutch health care insurance policy.[58] Issues of insurance coverage are not prohibitive for Dutch patients to participate in a clinical trial. Thus there is a need for specific clinical trials with innovative treatment approaches in patients who are not eligible for current clinical trials, particularly for elderly patients.

The introduction of ATRA in the mid-1980s dramatically changed the management of APL as it became a highly curable disease with cure rates exceeding 70% and early death rates around 10% in large clinical trials.[59,60] However, in our study and other population-based studies,[40,43] long-term survival was lower and early death rates substantially higher despite the availability of ATRA in clinical practice. Nevertheless, we show that survival of APL improved over time across all age groups, especially among patients older than 60 years of age, which partially might be explained by augmented disease awareness and use of anthracycline-based chemotherapy with concurrent ATRA as a standard of care in the Netherlands.[9]

Limitations of our study in AML and APL include changes in classification and registration practice over time. Detailed data on clinical (e.g. comorbidity and performance status) and disease-related characteristics (e.g. cytogenetics and molecular analysis) are not yet available in the NCR. Nevertheless, cancer registries remain the gold standard for ascertaining trends in incidence, treatment and survival in the general patient population.

In conclusion, in this comprehensive population-based study, we found that survival improved over the last two decades among patients with AML 70 years of age or younger and among patients with APL across all age groups. This is likely due to the increased use of intensive, curative treatment strategies. The inclusion of patients with AML in clinical trials decreased progressively with older age. Therefore, clinical trials that include geriatric and comorbidity indices should be specifically designed for the elderly AML population in order to establish evidence-based clinical practice guidelines.

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SUPPLEMENTARY METHODS

Registry and study population

The NCR is maintained and hosted by the Netherlands Comprehensive Cancer Organisation. The Netherlands Comprehensive Cancer Organisation is divided into nine regional networks. Each regional network is responsible for clinical consultations provided by university hospitals as well as potential treatment referral of leukemia patients from non-university to university hospitals. For the current study, region was defined according to the nine regional networks.

Treatment

Discrimination between an allogeneic (allo-SCT) and autologous stem cell transplantation (auto-SCT) was not possible with NCR data. Anonymous data on the type of SCT performed in the period 1989-2012 in the Netherlands were provided by the SCT Working Party of the Dutch-Belgian Cooperative Trial Group for Hemato-Oncology (HOVON). This data was linked to the NCR using the dates of birth and AML diagnosis, and sex. Ninety-three percent of this data could be linked to the NCR, whereas 7% of the SCT data from the NCR were not present in the data provided by the HOVON SCT Working Party. The missingness could be explained by systematic shortcomings in notification procedures and/or a delayed ascertainment of SCTs performed in the Netherlands to the HOVON SCT Working Party. For 7% of all SCT patients, the distinction between an auto- or allo-SCT could therefore not be made. In order to estimate the number of auto- and allo-SCTs for these unspecified SCTs, we used age group and year-specific proportions of auto- and allo-SCTs of the cases for which this information was available to extrapolate.

Treatment was described as the most intensive treatment the patient could receive. An auto- or allo-SCT is considered the most intensive treatment, followed by, in order of decreasing intensity, chemotherapy and supportive care. If a patient received supportive care only or chemotherapy according to NCR data, but received a SCT according to the data provided by the HOVON SCT Working Party, the SCT is reported instead (i.e. the most intensive treatment).

Trial participation

The NCR lacks information on trial participation of AML patients, and this information was obtained by linking databases of the HOVON and European Organization for Research and Treatment of Cancer (EORTC) cooperative clinical trial groups to the NCR using the dates of birth and AML diagnosis, and sex. Ninety-nine percent of both HOVON and EORTC data could be linked to the NCR. The trial data provided by the HOVON covers the study period 1989-2009, while the EORTC data covers the study period 1989-2007. As EORTC data were unavailable since 2008 onwards, we only consider the period 1989-2007 to analyze trial participation.

Trial participation was analyzed according to age group and period of accrual as HOVON and EORTC trials were not concomitantly open for all age groups during the whole study period. Consecutive HOVON and EORTC AML trials were concomitantly open for accrual throughout the period 1989-2007 for patients 60 years of age or younger. For patients over 60 years of age, there were consecutive HOVON and EORTC AML trials throughout the period 1989-1994. In 1995-1999, HOVON trials were not available for over 60-year-old patients. The next HOVON trial (HOVON 43) opened in October, 2000 and closed in June, 2006. During that same time frame, the EORTC 06933 trial closed in January, 2002; its successor (EORTC AML-17) opened in September, 2002. In the calendar years 2001, 2003, 2004, 2005 and 2007, HOVON and EORTC trials were concomitantly open for accrual. To prevent underestimating the rate of trial participation for over 60-year-olds, we restricted our analyses to periods where a trial was open for at least six months in every calendar year. Therefore, the period 1995-2000 and the calendar years 2002 and 2006 were not considered to analyze trial participation for over 60-year-olds. An overview of HOVON and EORTC clinical AML trials according to age group and accrual period that were used for this study is shown in Supplementary Table S2.

Trial participation of patients with APL was outside the scope of this study as clinical APL trials in the Netherlands were initiated by cooperative clinical trial groups other than HOVON and EORTC.

SUPPLEMENTARY RESULTS

Since the year 2001, secondary AML (that is, AML after MDS or MPN) was not standardly registered, because MDS and MPN were included in the registry as an incident case, whereas its progression to AML (that is, secondary AML) was not registered. Secondary AML was, however, standardly registered in the calendar period 2003-2009. The proportion of secondary AML in that particular calendar period was 6% in the overall series and increased with age. More specifically, the proportions of patients with secondary AML were 2%, 4%, 8%, 9% and 5% among all patients with AML aged 18-40, 14-60, 61-70, 71-80 and ≥80 years, respectively. To investigate the effect of secondary AML on survival, we included these cases in the primary AML sample in the calendar period 2003-2009. This analysis revealed that the effect of secondary AML on survival was negligible (less than 1 percent decrease in 5-year survival).

Supplementary Table S1. International Classification of Diseases for Oncology Third Edition (ICD-O-3) morphology codes for acute myeloid leukemia

AML subtype	ICD-O-3 code
AML with recurrent cytogenetic abnormalities	
t(15;17) - APL	9866
inv(16) or t(16;16)	9871
t(8;21)(q22;q22)	9896
t(9;11)(p22;q23)	9897
AML with multilineage dysplasia	9895
Therapy related AML	9920
AML, other	
Acute erythroid leukemia	9840
Acute myelomonocytic leukemia	9867
Acute basophilic leukemia	9870
AML, minimal differentiation	9872
AML, without maturation	9873
AML, with maturation	9874
Acute monocytic leukemia	9891
Acute megakaryoblastic leukemia	9910
Myeloid sarcoma	9930
Acute panmyelosis with myelofibrosis	9931
AML, NOS	9861

Abbreviations: AML, acute myeloid leukemia; APL: acute promyelocytic leukemia; NOS, not otherwise specified.

Supplementary Table 2. HOVON and EORTC clinical AML trials

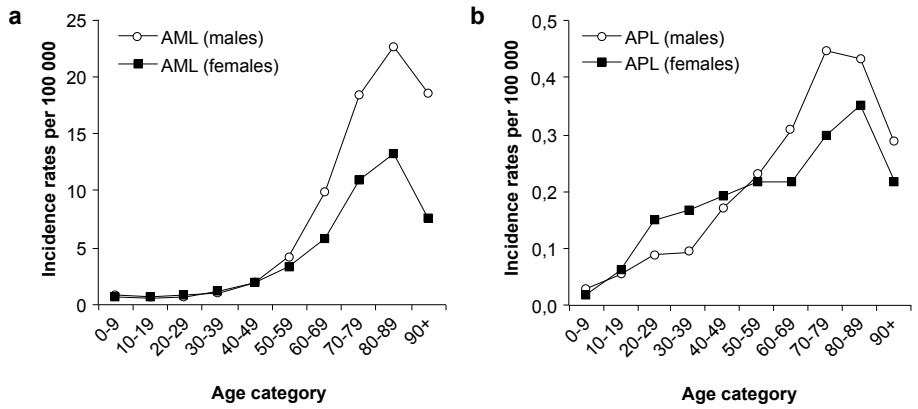
Trial group	Trial name	Accrual period (month/year)	Age limits (years)	Therapy-related AML excluded?
HOVON	HOVON 4	07/1987 - 06/1995	15-60	Unknown
	HOVON 4A	10/1990 - 11/1994	15-60	Unknown
	HOVON 29	03/1995 - 06/2001	18-60	Yes
	HOVON 42	01/2001 - 02/2007	18-60	No[a]
	HOVON 42A	01/2006 - 10/2008	18-60	No[a]
	HOVON 43	10/2000 - 06/2006	>60	No[a]
	HOVON 81	02/2007 - 08/2009	>60	No[b]
EORTC	EORTC 06863 (AML-8A)	11/1986 - 06/1994	10-44	No
	EORTC 06864 (AML-8B)	11/1986 - 06/1994	45-60	No[c]
	EORTC 06931 (AML-10)	11/1993 - 07/2000	15-60	No[c]
	EORTC 06954 (AML-13)	12/1995 - 11/2001	61-80	No[c]
	EORTC 06991 (AML-12)	07/1999 - 06/2008	15-60	No[c]
	EORTC 06993 (AML-15)	06/2000 - 01/2002	≥61	No[c]
	EORTC 06012 (AML-17)	09/2002 - 08/2007	61-75	No
HOVON & EORTC	HOVON 9/EORTC 06862	04/1986 - 11/1993	>60	Unknown
	HOVON 11/EORTC 06892	11/1990 - 10/1994	>60	No

[a] Patients with therapy-related AML were only eligible provided they have not received chemotherapy during the past 6 months before randomization [b] Patients with therapy-related AML were only eligible provided they have not received chemotherapy during the past 2 years before randomization. [c] Only patients with a progressive malignant disease, other than their leukemia, were excluded.

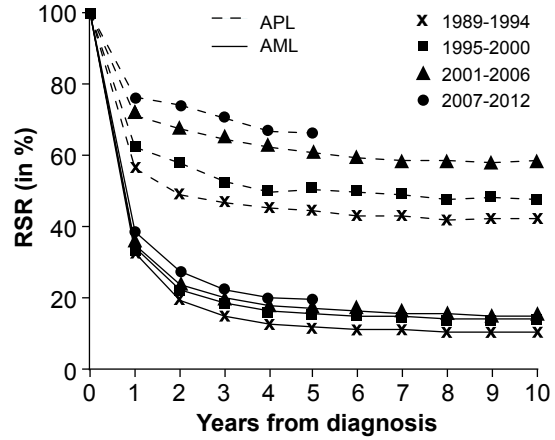
Supplementary Table S3. Probability of early death among patients diagnosed with AML and APL in the Netherlands, 1989-2012

Disease type	Independent variable	Univariable		Multivariable	
		OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
AML	**Sex**				
	Male	1.00 (ref)		1.00 (ref)	
	Female	1.06 (0.97-1.15)	0.180	1.04 (0.95-1.14)	0.350
	Age, years				
	18-40	1.00 (ref)		1.00 (ref)	
	41-60	1.60 (1.26-2.04)	< 0.001	1.45 (1.14-1.85)	0.003
	61-70	3.06 (2.42-3.85)	< 0.001	2.24 (1.77-2.85)	< 0.001
	>70	7.47 (5.99-9.30)	< 0.001	4.04 (3.21-5.09)	< 0.001
	Calendar period				
	1989-1994	1.00 (ref)		1.00 (ref)	
	1995-2000	1.00 (0.92-1.17)	0.580	1.03 (0.90-1.17)	0.680
	2001-2006	0.93 (0.82-1.05)	0.230	0.89 (0.78-1.02)	0.085
	2007-2012	0.85 (0.75-0.96)	0.008	0.79 (0.69-0.89)	< 0.001
	Hospital type				
	Non-university	1.00 (ref)		1.00 (ref)	
	University	0.21 (0.19-0.24)	< 0.001	0.34 (0.31-0.38)	< 0.001
APL	**Sex**				
	Male	1.00 (ref)			
	Female	1.00 (0.66-1.50)	0.990		
	Age, years				
	18-40	1.00 (ref)		1.00 (ref)	
	41-60	2.12 (1.08-4.15)	0.028	1.92 (0.98-3.80)	0.060
	61-70	2.77 (1.28-5.97)	0.009	2.51 (1.15-5.46)	0.020
	>70	6.94 (3.55-13.60)	< 0.001	4.91 (2.41-9.97)	< 0.001
	Calendar period				
	1989-1994	1.00 (ref)			
	1995-2000	1.25 (0.66-2.25)	0.490		
	2001-2006	0.88 (0.47-1.65)	0.700		
	2007-2012	0.84 (0.45-1.55)	0.570		
	Hospital type				
	Non-university	1		1	
	University	0.34 (0.22-0.51)	< 0.001	0.50 (0.32-0.79)	0.003

Abbreviations: OR, odds ratio; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia.

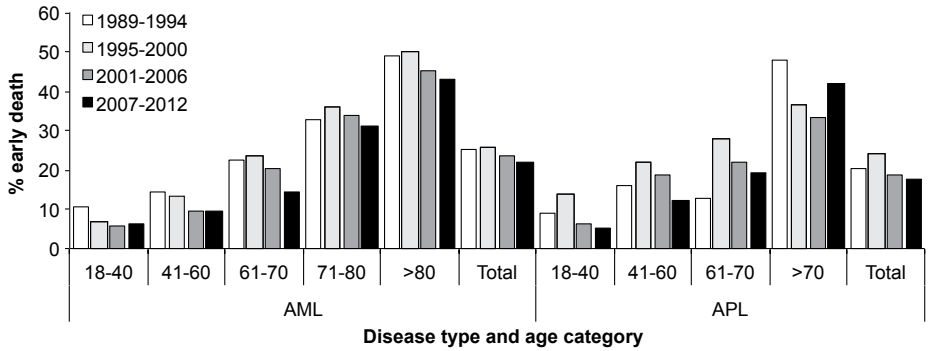


Supplementary Figure S1. Age-specific incidence rates of (**a**) AML and (**b**) APL in the Netherlands according to sex, 1989-2012.

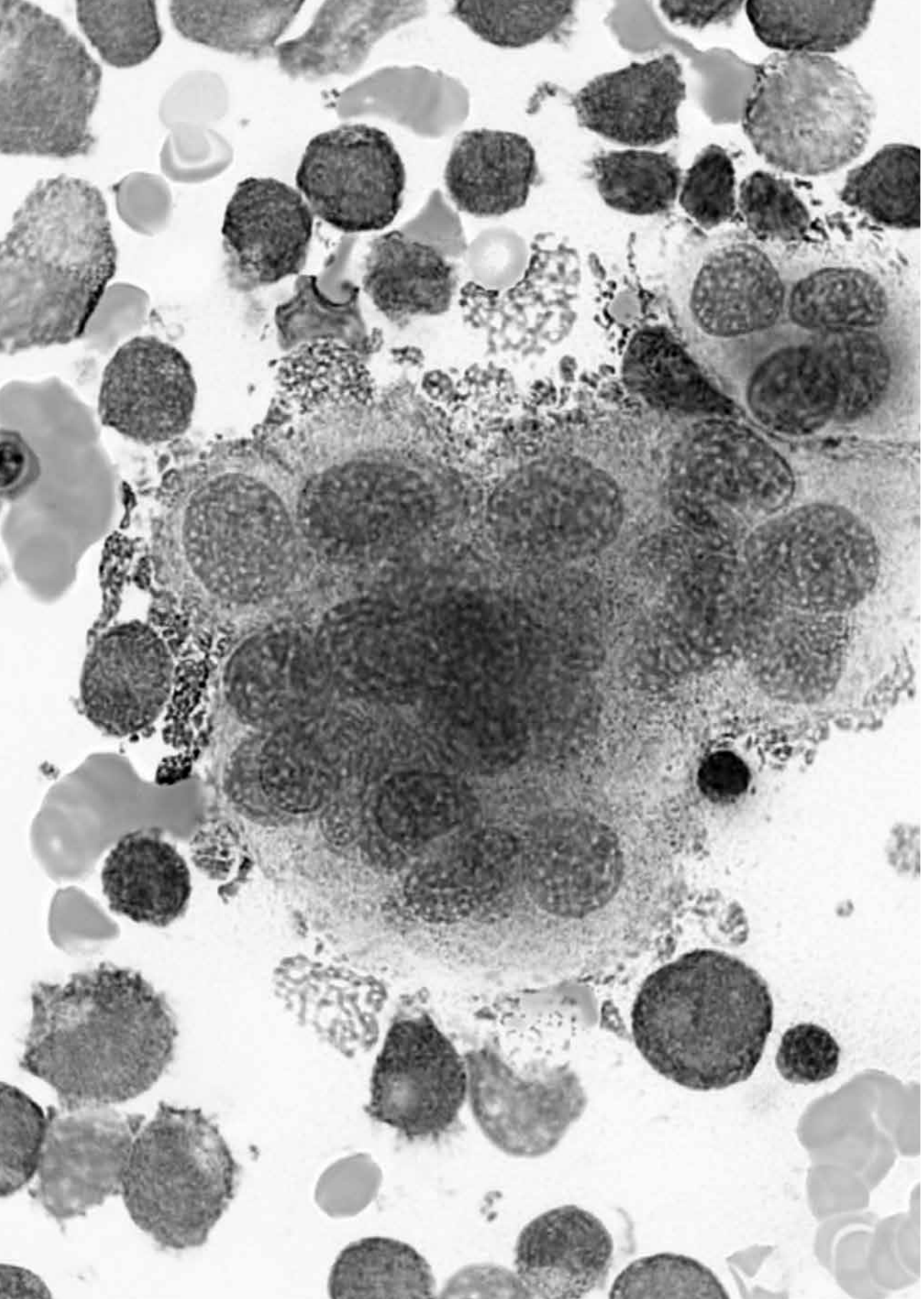


Disease type	Calendar period	RSR (in %) with 95% CI		
		1-year	5-year	10-year
APL	1989-1994	56 (46-65)	45 (35-54)	42 (32-52)
	1995-2000	62 (53-70)	50 (42-59)	48 (39-57)
	2001-2006	71 (64-77)	61 (53-68)	58 (50-66)
	2007-2012	76 (70-82)	66 (58-74)	-
AML	1989-1994	33 (31-35)	12 (11-14)	11 (9 -12)
	1995-2000	35 (33-36)	16 (14-17)	14 (13-16)
	2001-2006	35 (34-37)	17 (16-19)	15 (14-17)
	2007-2012	39 (37-40)	20 (18-21)	-

Supplementary Figure S2. Relative survival rates (RSRs) of adult patients diagnosed with AML (solid line) and APL (dashed line) in the Netherlands according to calendar period of diagnosis, 1989-2012. The table presents the projected 1-, 5- and 10-year RSRs with 95% confidence intervals (CIs) according to calendar period of diagnosis.



Supplementary Figure S3. Early death rates of patients with AML and APL in the Netherlands according to age at diagnosis and calendar period of diagnosis, 1989-2012. Early death is defined as death within 30 days from diagnosis.



The use of medical claims to assess incidence, diagnostic procedures and initial treatment of myelodysplastic syndromes and chronic myelomonocytic leukemia in the Netherlands

5

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ABSTRACT

Myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemia (CMML) may be underreported in cancer registries such as the Netherlands Cancer Registry (NCR). Analysis of Dutch medical claims can complement NCR data on MDS and CMML. We analyzed data on 3681 MDS patients and 235 CMML patients aged ≥18 years with initial claims for MDS or CMML from the Dutch nationwide medical claims-based Diagnosis Treatment Combination Information System (DIS) between 2008-2010. Clinical information was available in the DIS. MDS and CMML were diagnosed without a bone marrow (BM) examination in almost half of the patients. The age-standardized incidence rate (ASR) per 100,000 in the cohort that underwent BM examinations compared with NCR data was 2.8 *vs*. 3.3 for MDS and 0.2 *vs.* 0.4 for CMML in 2008-2010. A conservative treatment approach was associated with increasing age and absence of BM examination in MDS ($p < 0.001$ for both) and CMML patients ($p < 0.033$ for both). In conclusion, the ASR of MDS in the cohort that underwent BM examinations was comparable with the NCR. The majority of elderly patients, either with or without BM examinations, received no therapy. Together, MDS and CMML may be misdiagnosed and inappropriately managed without a BM confirmation.

INTRODUCTION

Myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemia (CMML) comprise a diverse group of clonal hematopoietic stem cell disorders, which are both characterized by ineffective hematopoiesis and an increased risk of leukemic progression.[1,2] Based on the few available data from large population-based cancer registries, the age-standardized incidence rate ranges from 2.0 to 3.4 per 100,000 for MDS and from 0.3 to 0.4 per 100,000 for CMML in Western countries.[3-7] Both malignancies largely affect older people as the age-specific incidence rate increases in parallel with older age.[3-7] Notification of MDS and CMML cases to population-based cancer registries is principally based on bone marrow confirmed cases as morphological assessment of the bone marrow forms the cornerstone in the diagnostic work-up of MDS and CMML.[8-11]

Recent data from the few available medical claims-based studies suggested that elderly patients with MDS and other myeloid malignancies were underreported in population-based cancer registries of the U.S. SEER program[12-14] and Australia.[15,16] The incidence of MDS in those studies was approximately 2 to 4 times higher compared with data from cancer registries.[13-16] This may also hold true for the nationwide population-based Netherlands Cancer Registry (NCR). The abovementioned medical claims-based studies, however, have limitations obscuring interpretation and broad applicability of the results, including the inability to identify people without medical insurance,[13,14] the inclusion of selected beneficiaries based on the type of medical coverage,[13,14] and inclusion of MDS cases without bone marrow examinations as incident cases.[15,16]

By contrast, all residents of the Netherlands are legally obliged to take out a Dutch healthcare insurance. Besides, Dutch medical claims data includes information on diagnostic procedures and initial treatment decisions, thereby overcoming several, although not all, of the abovementioned limitations. For that reason, population-based analysis of Dutch medical claims might complement NCR data on MDS and CMML. We conducted a nationwide medical claims-based study among adult patients with MDS and CMML in the Netherlands between 2008 and 2010. The aims of the study were to assess incidence, diagnostic procedures and initial treatment among these patients.

PATIENTS AND METHODS

Dutch Healthcare Insurance

All residents of the Netherlands are legally obliged to take out a healthcare insurance policy for the standard package. The standard package mainly includes inpatient and outpatient care, physician services (general practitioners and medical specialists), medication, durable medical equipment, home health care and hospice care. All policy-holders are charged with a flat-rate premium for the standard package.

Data Source and Study Population

All activities that were performed to diagnose and treat a patient are registered by the hospital into one care package for billing purposes, namely into a *Diagnose Behandeling Combinatie* (DBC; Diagnosis Treatment Combination) package. A DBC package is a medical claim that is initiated when a specific diagnosis is made and a particular treatment is started. All data regarding activities and resulting DBC packages are reported by the hospital at the time of billing for services to the DBC Information System (DIS), which also maintains all data that has been sent. Upon request for scientific research, the DIS provides a fully de-identified minimal dataset of DBC medical claims which is in accordance with the Dutch Data Protection Act. The minimal dataset contains information on demographic characteristics, diagnosis, hospital type (university or non-university hospital), claim type (initial or subsequent claim), claim initiation date, treatment decision and all activities that were performed. Diagnoses within DBC packages were developed by each specialism separately instead of using existing codes for diseases as listed in the 10th revision of the International Statistical Classification of Diseases and Related Health Problems.[17]

We identified patients with MDS and CMML aged 18 years or older between 2008 and 2010 from the DIS using DBC diagnosis codes 763 (refractory anemia with excess blasts; RAEB) and 762 (MDS, not otherwise specified; MDS NOS) for MDS, and 773 for CMML. The DBC codes for MDS and CMML are based on the disease definitions of the World Health Organization classification of hematological malignancies.[18,19] MDS subtypes other than RAEB are categorized as MDS NOS. The study period between 2008 and 2010 was chosen to compare our data with the NCR as incidence rates of MDS according to the NCR remained stable during that period.[7] For the current study, we exclusively included cases with initial DBC claims (*zorgtype* 11 medical claims) and excluded cases with subsequent DBC claims (*zorgtype* 21 medical claims) after the initial claim. Initial claims were considered as newly diagnosed cases and the initiation date of the initial claim was regarded as the date of diagnosis. We applied the abovementioned exclusion criteria to omit prevalent cases (i.e. subsequent claims) for measuring the disease incidence.

Diagnostic and Treatment Activities

Bone marrow examinations are essential for the correct diagnosis of MDS and CMML as recommend by international expert panels.[8-11] The diagnoses in the DBC cohort cannot be pathologically confirmed due to the anonymous data provided by the DIS; therefore, we cannot obtain diagnostic information by retrospective medical record reviews. To assess whether the diagnoses were made by examining bone marrow, we noted DBC activity codes used to claim services for bone marrow examinations (38407, 38497-38499, 50501, 50503, 70710, 77102 or 120095) as a surrogate for pathological confirmation. The DBC activity codes are selected by physicians at the time of billing for services. Treatment for MDS and CMML in the DIS is defined as patients who receive no therapy, supportive care, chemotherapy alone, allogeneic stem cell transplantation (allo-SCT), and other or unspecified therapy.

No clinical data were available for our cohort such as classification, prognostication, time to leukemic transformation, vital statistics and detailed information on treatment.

Statistical Analyses

Age-standardized incidence rates (ASRs) by sex were calculated per 100,000 person-years for MDS and CMML using the annual mid-year population size as obtained from Statistics Netherlands. Incidence rates were age-standardized to the European standard population. Further, we calculated age-specific incidence rates for five age categories.

Characteristics of patients who underwent bone marrow examinations or those who did not were compared with the Pearson chi-square test and the chi-square test for trend for discrete variables, and the Kruskal-Wallis test for continuous variables. Multivariable logistic regression was used to test for the association of a particular treatment strategy on age and bone marrow performance status. A *p*-value less than 0.05 was considered statistical significant. All statistical analyses were performed with STATA Statistical Software Release version 12.0 (College Station, TX)

RESULTS

Incidence of MDS and CMML

We identified a total of 3681 patients with MDS and 235 patients with CMML from the DIS during the study period of 2008-2010. Characteristics and ASRs of these patients are shown in Table 1 (total cohort). The overall ASR of MDS was 5.4 per 100,000 in 2008-2010. Incidence rose very steeply with older age, with the highest incidence among patients aged 80 years and older (84.4 per 100,000). The overall ASR of MDS among males (7.0 per 100,000; 95% CI, 6.7-7.3) was higher than females (3.9 per 100,000; 95% CI, 3.7-4.1), which was mainly ascribed to the higher incidence in the over 70-year old men compared with the equivalent female group (Fig. 1A; total cohort).

Incidence rates of CMML were much lower than those of MDS, with an overall ASR of 0.4 per 100,000 in 2008-2010 (Table 1; total cohort). The incidence of CMML was the highest among the over 80-year-old patients (3.8 per 100,000) and higher among males (0.5 per 100,000; 95% CI, 0.4-0.6) than females (0.2 per 100,000; 95% CI, 0.2-0.3).

Bone marrow examinations in MDS and CMML

Information regarding the performance of bone marrow examinations was available for 3628 (98.6%) patients with MDS and 232 (98.7%) patients with CMML. MDS and CMML were diagnosed without performing a bone marrow examination in 46% and 44% of the patients, respectively. The proportion of patients with MDS and CMML who did not undergo a bone marrow examination was 48% and 50% in non-university hospitals and 40% and 28% in university hospitals, respectively. Patients with MDS who did not undergone bone marrow examinations at diagnosis were older (median age 79 *vs.* 74; $p < 0.001$; Fig. 2A) and more likely to be female (50.9% *vs.* 41.9%; $P<.001$) compared with those who underwent. Similar patterns were also observed for patients with CMML but the difference in age (median age 74 *vs.* 72; $p = 0.078$; Fig. 2B) and between females and males (47.1% *vs.* 41.5%; $p = 0.410$) were not statistically significant.

Table 1. Characteristics of patients with myelodysplastic syndromes and chronic myelomonocytic leukemia in the DIS, 2008-2010.

		Disease type											
		RAEB			MDS NOS			MDS (total)[a]			CMML		
Cohort	Characteristics	No.	%	ASR[b]	No.	%	ASR[b]	No.	%	ASR[b]	No.	%	ASR[b]
Total cohort	**Total**	406		0.64	3275		4.79	3681		5.44	235		0.37
	Sex												
	Male	252	62.1	0.85	1854	56.6	6.16	2106	57.2	7	149	63.4	0.5
	Female	154	37.9	0.44	1421	43.4	3.43	1575	42.8	3.87	86	36.6	0.24
	Age, years												
	Median	72			77			77			73		
	18-49	33	8.1	0.09	125	3.8	0.35	158	4.3	0.44	10	4.3	0.03
	50-59	38	9.4	0.55	206	6.3	2.99	244	6.6	3.54	23	9.8	0.34
	60-69	109	26.8	2.03	550	16.8	10.29	659	17.9	12.32	53	22.6	0.99
	70-79	135	33.3	4.2	1092	33.3	33.2	1227	33.3	37.4	88	37.4	2.76
	≥80	91	22.4	5.74	1302	39.8	78.62	1393	37.8	84.36	61	26.0	3.8
	Hospital type												
	Non-university	269	66.3	-	2959	90.4	-	3228	87.7	-	177	75.3	-
	University	137	33.7	-	316	9.6	-	453	12.3	-	58	24.7	-
BM only cohort	**Total**	276		0.45	1693		2.57	1969		3.02	131		0.21
	Sex												
	Male	180	65.2	0.61	1028	60.7	3.4	1208	61.4	4	86	65.6	0.28
	Female	96	34.8	0.29	665	39.3	1.74	761	38.6	2.03	45	34.4	0.13
	Age, years												
	Median	70			75			74			72		
	18-49	25	9.1	0.07	78	4.6	0.22	103	5.2	0.28	5	3.8	0.01
	50-59	30	10.9	0.43	131	7.7	1.9	161	8.2	2.34	17	13.0	0.25
	60-69	81	29.3	1.51	335	19.8	6.27	416	21.1	7.78	30	22.9	0.56
	70-79	91	33.0	2.86	646	38.2	19.72	737	37.4	22.58	49	37.4	1.58
	≥80	49	17.8	3.13	503	29.7	30.88	552	28.0	34.01	30	22.9	1.89
	Hospital type												
	Non-university	179	64.9	-	1518	89.7	-	1697	86.2	-	89	67.9	-
	University	97	35.1	-	175	10.3	-	272	13.8	-	42	32.1	-

RAEB, refractory anemia with excess blasts; MDS NOS, myelodysplastic syndromes not otherwise specified; CMML, chronic myelomonocytic leukemia; ASR, age-standardized incidence rate; BM, bone marrow. [a] Includes patients with MDS NOS and RAEB. [b] Age-standardized to the European standard population and presented per 100,000 person-years.

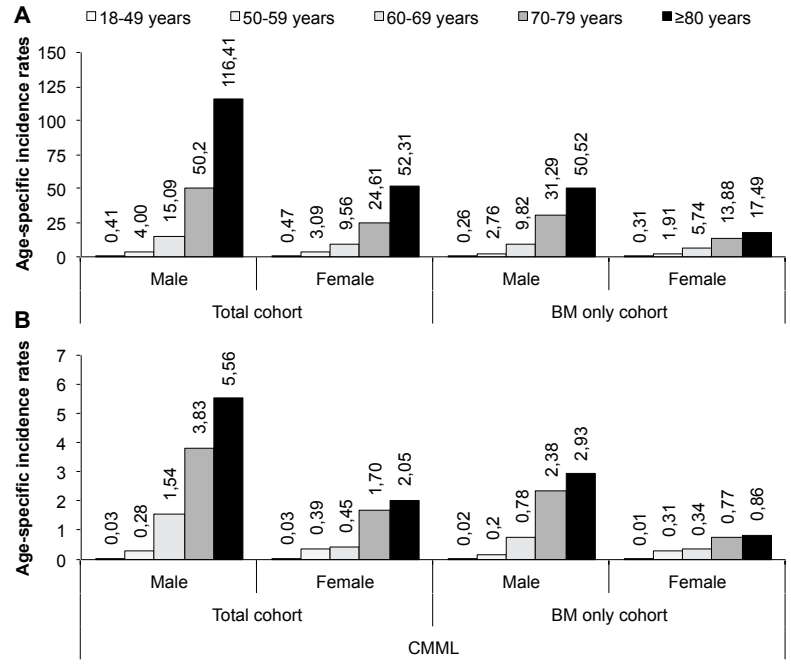

Figure 1. Age-specific incidence rates of (A) MDS and (B) CMML according to cohort type (total cohort *vs*. BM only cohort), age and sex, 2008-2010.

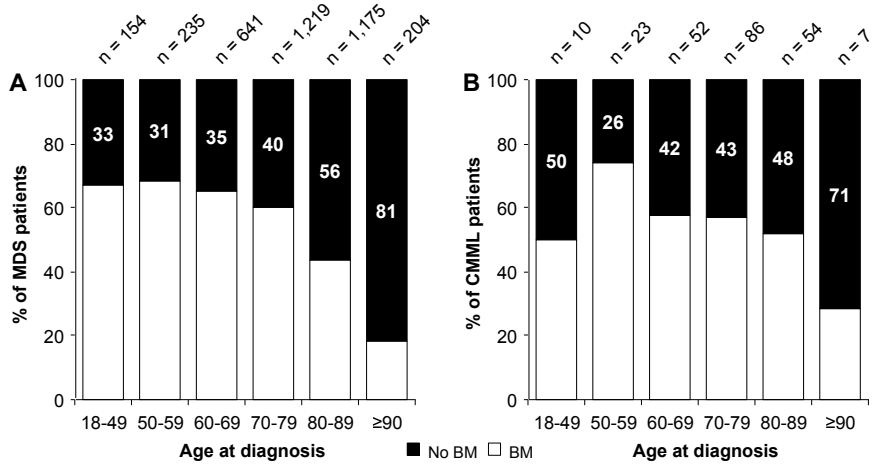

Figure 2. The performance of bone marrow (BM) examinations in (A) MDS and (B) CMML patients with initial DBC claims according to age at diagnosis, 2008-2010. Data are shown for 3628 MDS patients and 232 CMML patients with available data regarding the BM performance status. The performance of bone marrow examinations decreased statistically significantly in parallel with older age category in patients with MDS (p for trend < 0.001) but not in patients with CMML (p for trend = 0.128).

Demographic characteristics and ASRs among patients with MDS and CMML who underwent bone marrow examinations at diagnosis are shown in Table 1 (BM only cohort). The overall ASR of MDS and CMML in that cohort was 3.0 and 0.2 per 100,000 during the study period of 2008-2010, respectively. A comparison with population-based data from the NCR revealed that the overall ASR of MDS in our study was almost 2-fold higher than the NCR, namely 5.4 *vs*. 3.3 per 100,000 in 2008-2010.[20] However, rates were almost equal if only cases with bone marrow examinations were selected in our cohort, namely 3.0 *vs*. 3.3 per 100,000. The overall ASR of CMML in 2008-2010 was 0.4 per 100,000 according to our study and NCR data. However, the ASR in the cohort with bone marrow examinations only was 2-fold lower than the NCR, namely 0.2 *vs*. 0.4 per 100,000.[20]

Initial treatment in MDS and CMML

Initial treatment by bone marrow performance status, disease type and age categories are shown in Table 2. A conservative treatment strategy (i.e. no treatment + supportive care) in patients with MDS and CMML was associated with increasing age (odds ratio [OR], 1.02; 95% CI, 1.01-1.03; $p < 0.001$ and 1.03; 95% CI, 1.00-1.06; $p = 0.032$, respectively) and absence of bone marrow examination (OR, 1.76; 95% CI, 1.38-2.24; $p < 0.001$ and 2.69; 95% CI, 1.31-5.53; $p = 0.007$, respectively).

The following results are described for the cohort of patients who underwent bone marrow examinations. Antineoplastic therapy (i.e. chemotherapy alone + allo-SCT) was less frequently provided in patients with MDS NOS than in patients with RAEB (3% *vs.* 22%; $p < 0.001$) and CMML (3% *vs.* 21%; $p < 0.001$). The use of antineoplastic therapy was mainly restricted to patients younger than 65 years, especially the application of allo-SCT.

Table 2. Initial treatment of myelodysplastic syndromes and chronic myelomonocytic leukemia in the Netherlands by bone marrow performance status and age at diagnosis, 2008-2010.

	No bone marrow				Bone marrow			
Age at diagnosis	**18-64**	**65-79**	**≥80**	**Total**	**18-64**	**65-79**	**≥80**	**Total**
Initial treatment	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**
Total No. MDS (total)[a]	*n* = 220	*n* = 612	*n* = 827	*n* = 1659	*n* = 442	*n* = 975	*n* = 552	*n* = 1969
No therapy	75	69	61	66	69	67	63	66
Supportive care	16	24	34	28	14	22	29	22
Chemotherapy	1	1	0	1	7	5	2	4
Allo-SCT	3			0	5	0		1
Other therapy	5	5	5	5	6	6	7	6
Total No. RAEB	*n* = 21	*n* = 53	*n* = 41	*n* = 115	*n* = 90	*n* = 137	*n* = 49	*n* = 276
No therapy	52	57	27	45	46	46	57	48
Supportive care	29	34	73	47	12	30	31	24
Chemotherapy	5	6		3	23	18	8	18
Allo-SCT	10			2	12			4
Other therapy	5	4		3	7	6	4	6
Total No. MDS NOS	*n* = 199	*n* = 559	*n* = 786	*n* = 1544	*n* = 352	*n* = 838	*n* = 503	*n* = 1693
No therapy	77	70	63	67	74	70	63	69
Supportive care	15	23	32	26	14	21	28	22
Chemotherapy	1	1	1	1	3	2	1	2
Allo-SCT	2			0	3	0		1
Other therapy	5	6	5	5	6	6	7	6
Total No. CMML	*n* = 21	*n* = 49	*n* = 31	*n* = 101	*n* = 35	*n* = 66	*n* = 30	*n* = 131
No therapy	76	57	52	59	51	58	63	57
Supportive care	10	29	42	29	11	15	20	15
Chemotherapy	10	12	6	10	26	18	13	19
Allo-SCT					9			2
Other therapy	5	2		2	3	9	3	6

MDS NOS, myelodysplastic syndromes, not otherwise specified; Allo-SCT, allogeneic stem cell transplantation; RAEB, refractory anemia with excess blasts; CMML, chronic myelomonocytic leukemia. [a] Includes patients with MDS NOS and RAEB

DISCUSSION

The overall ASR of MDS in this medical claims-based study was nearly 2-fold higher than population-based data from the NCR.[7,20] Interestingly, incidence rates between this study and the NCR were in good agreement if only cases with bone marrow examinations were selected in our study.[20] The few recent medical claims-based studies suggested that MDS cases were underreported in population-based cancer registries of the U.S. SEER program[14] and Australia.[15,16] The magnitude of underreporting could slightly be overestimated in these medical claims-based studies as the Australian studies included MDS cases without bone marrow examinations as incident cases[15,16] and the U.S. Medicare studies used specific inclusion and exclusion criteria regarding the age of the beneficiaries and the type of medical coverage.[13,14,21] Our study avoided several, although not all, of the abovementioned limitations. We most likely identified all adult patients because all residents of the Netherlands are legally obliged to takeout a Dutch medical insurance. By using a nationwide medical claims-based cohort, we identified all adult patients who were given the diagnostic code of MDS in routine clinical practice irrespective of the diagnostic procedures.

Large nationwide population-based studies based on data from cancer registries and medical claims are currently lacking in CMML. The few available smaller studies had limitations such as a short study period or a cohort only partially covering the country.[4,6,22-25] The overall ASR of CMML in the cohort of patients who underwent bone marrow examinations was half as low as the ASR in the NCR.[20] A possible explanation of this discrepancy could be that the NCR also ascertains CMML cases that are diagnosed by the physician solely based on the peripheral blood examination (i.e. blood test and blood smear). However, bone marrow examinations are essential to establish or exclude the diagnosis of CMML as well as MDS.[8-11] Both malignancies may be misdiagnosed without bone marrow confirmation.

Approximately half of the patients with MDS and CMML in our study were given the diagnosis without performing a bone marrow examination. However, peripheral blood features suggestive of a MDS or CMML, such as cytopenias and dysplastic features in one or more cell lineages or persistent peripheral blood monocytosis as an additional diagnostic characteristic of CMML, are not exclusive for MDS or CMML.[26] Cytopenias are common among the elderly community, especially anemia.[27] It seems unlikely that all cases without bone marrow examinations in our study were truly MDS or CMML as this group may be given the diagnosis without further diagnostic work-up after abnormal full blood counts. Therefore, it is important to exclude other (malignant) disorders and reactive causes of cytopenias, dysplasia and monocytosis in the diagnostic work-up of MDS and CMML.

As expected, treatment approaches in elderly patients as well as in patients without bone marrow examinations were conservative in our study. Elderly patients are by definition not suitable candidates for intensive and potentially curative therapy.[9-11] However, less intensive disease-modifying treatment modalities became recently available in the Netherlands for these elderly patients. More specifically, lenalidomide was registered in 2013 for use in MDS with an isolated del(5q).[28] and azacitidine was registered in 2009 for use in high-risk MDS and CMML.[29]

Therapeutic decision-making in MDS and CMML rely on outcomes from diagnostic procedures such as the bone marrow blast count, karyotype and the number of cytopenias.[9-11] These and other prognostic parameters are incorporated in disease-specific prognostic scoring systems to risk stratify patients[30-33] and to guide risk-adapted treatment decision making.[9-11] The absence of bone marrow examination in almost half of our patients might result in inaccurate risk-stratification, thereby possibly leading to inappropriate management. Therefore, all essential diagnostic procedures should be performed in every patient to ensure accurate prognostication and to guide appropriate risk-adapted therapeutic decision-making.[9-11]

Several limitations of our study should be discussed. Our medical claims-based data are anonymous in accordance with the Dutch Data Protection Act. Therefore, it cannot be linked to the NCR to assess whether cases in the present study were truly MDS or CMML. Also, we cannot pathologically confirm individual diagnoses due to lack of relevant diagnostic information in the DIS. Medical claims-based studies can complement cancer registry data but cancer registries remain the gold standard in any rational program of cancer surveillance.

In conclusion, the overall ASR of MDS was nearly 2-fold higher than population-based data from the NCR. This discrepancy is mainly due to the large proportion of diagnoses without bone marrow examinations in our medical claims-based study. The majority of elderly patients and patients without bone marrow examinations received no therapy. This may be explained by the limited availability of therapeutic agents and absence of prognostic information gained by bone marrow examination to guide risk-adapted therapy. Collectively, MDS and CMML may be misdiagnosed in the absence of bone marrow confirmation, and therefore might be inappropriately managed due to the inaccurate diagnosis.

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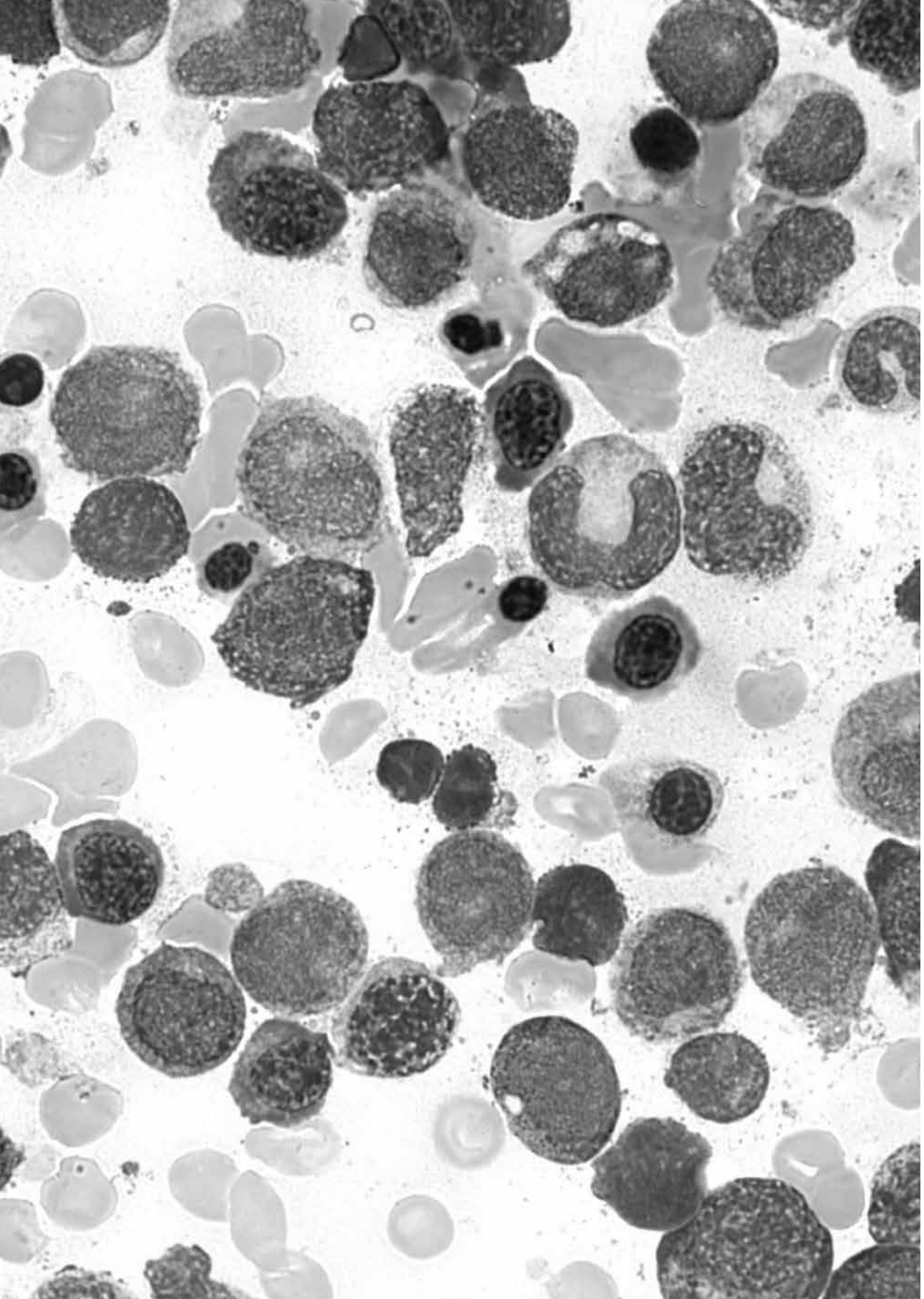

Diagnosis and treatment of myelodysplastic syndromes and chronic myelomonocytic leukemia in daily practice: results from the Dutch population-based PHAROS MDS registry

6

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ABSTRACT

The Dutch PHAROS MDS registry was established to provide additional data on clinical characteristics of patients with myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemia (CMML) complementary to the dataset of the nationwide Netherlands Cancer Registry. In this population-based study, we assessed patterns of diagnostic procedures and disease management among 676 MDS (median age, 75 years) and 102 CMML patients (median age, 74 years) diagnosed between 2008-2011 and recorded in the PHAROS MDS registry. That registry essentially covers the west part of the Netherlands (approximately 6.3 million inhabitants). All diagnoses were based on bone marrow assessment. For MDS and CMML together, the degree of dysplasia in erythroid, granulocytic and megakaryocytic lineages were, respectively, reported in 33%, 43% and 30% of evaluable bone marrow aspirates. Cytogenetic assessments were, respectively, performed in 54% and 58% of MDS and CMML patients, and decreased progressively with older age. The International Prognostic Scoring System (IPSS) could not be determined for 55% of MDS patients, primarily owing to unperformed cytogenetics. These patients were less likely to receive anti-neoplastic therapy compared to MDS patients with established IPSS risk scores. In conclusion, this study indicates that particular diagnostic and prognostic procedures that are essential for the diagnosis and subsequent treatment-decision making of MDS and CMML were not fully utilized. Well-established population-based registries are useful instruments to evaluate guideline adherence and may be part of guideline development.

INTRODUCTION

Myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemia (CMML) are related, albeit distinct, hematological malignancies characterized by ineffective hematopoiesis and a propensity for leukemic progression.[1,2] Both malignancies primarily affect the elderly, as the median age at diagnosis is around 70 to 75 years.[3-6]

Clinical practice guidelines for the diagnosis and treatment of MDS and CMML are mainly based on findings from uncontrolled, non-randomized, multicenter clinical studies.[7,8] Therefore, most findings to guide clinical decision-making in MDS and CMML are based on evidence that is generally biased towards patients who might not entirely reflect the actual MDS and CMML population at large. Information gained from well-designed population-based studies can be used to validate findings from clinical studies and to evaluate guideline adherence in daily practice.[9,10] At present, there are only a few studies that have provided comprehensive insight into the delivery of care to MDS and CMML patients at the population level.[11-15] These studies, however, were prone to selection and/or referral biases, which perhaps may not reflect the actual clinical practice. Obviously, studies covering all patients within a well-defined geographic area would diminish these biases.

Here we report the outcomes of a comprehensive, retrospective, population-based cohort study among newly diagnosed MDS and CMML patients within a well-defined area in the Netherlands. The aim of the study was to assess baseline characteristics, and patterns of diagnostic procedures and disease management among these patients in daily practice.

PATIENTS AND METHODS

Registries and study population

The Dutch **P**opulation-based **HA**ematological **R**egistry for **O**bservational **S**tudies (PHAROS) in MDS and CMML—the PHAROS MDS registry—was established to document additional data on various demographic, clinical, disease and treatment characteristics next to the dataset of the nationwide population-based Netherlands Cancer Registry (NCR). Details about the registries as well as their validity, logistics and completeness were previously reported.[4,16] In brief, the PHAROS MDS registry relies on the NCR for case notification. The NCR, which is maintained and hosted by the Netherlands Comprehensive Cancer Organisation (IKNL), has an overall coverage of at least 95% of all newly diagnosed malignancies in the Netherlands, and primarily receives notification from the Nationwide Network of Histopathology and Cytopathology and the National Hospital Discharge Registry.[17] The PHAROS MDS registry is an initiative of the Dutch-Belgian Hemato-Oncology Group (HOVON), the institute of Medical Technology Assessment at the Erasmus University Rotterdam and IKNL.[16] This study was approved by the Ethics Committee of the Erasmus University Medical Center.

The PHAROS MDS registry includes adult (>18 years) patients diagnosed with MDS and CMML in the Netherlands between January, 2008 and December, 2011. In addition, like the NCR, it exclusively includes cases that were confirmed through bone marrow (BM) by the physician and classified according to the World Health Organization (WHO) criteria (i.e. <20% BM blasts).[18] Due to the retrospective nature of this study, central review of BM specimens was not possible. The PHAROS MDS registry essentially covers the west part of the Netherlands with 6.3 million people (~40% of the Dutch population). This area includes 3 university hospitals and 27 non-university hospitals.

Prognostic scoring systems and treatment definitions

Prognostic scoring systems for MDS that are recommended by the European Leukemia Network (ELN) are the International Prognostic Scoring System (IPSS) and its revision (IPSS-R).[7,19,20] In the present study, we applied these scoring systems to assess their prognostic value in our patient population. In addition, we also applied the age-adjusted IPSS-R.[20] In this study, we defined lower-risk MDS as those with IPSS low or intermediate-1 risk, whereas higher-risk MDS as those with IPSS intermediate-2 or high risk. As for CMML, the CMML-specific Prognostic Scoring System (CPSS) was used.[21] The molecular-based prognostic scoring system for CMML devised by Itzykson *et al*. could not be utilized, as assessment of *ASXL1* mutational status was not routinely performed for the diagnosis of CMML during the study period.[22]

Anti-neoplastic therapy was defined as patients who received hydroxyurea, lenalidomide, azacitidine, intensive chemotherapy or allogeneic stem cell transplantation (alloSCT) during the course of their disease. Information on treatment after leukemic progression, that is, ≥20% blasts in the peripheral blood and/or BM, is not available for the present study.

Statistical analyses

Categorical variables were compared with the Pearson chi-square test and the chi-square test for trend, whereas continuous variables with the Kruskal-Wallis test. A multivariable logistic regression analysis was performed to analyze potential predictors that were associated with (i) cytogenetic assessments and (ii) application of anti-neoplastic therapy. Only variables with $P<0.10$ in univariable analysis were included in multivariable analysis. Results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). The correlation between categorical variables was assessed with the Kendall's tau correlation coefficient. Overall survival (OS) was measured with the Kaplan-Meier method from time of diagnosis to death or last follow-up, and compared with the log-rank test. The discriminative ability of each prognostic scoring system was assessed using the Harrell's concordance index (C-index).[23] The C-index estimate can range from no discrimination (0.0) to perfect discrimination (1.0). A two-sided $P<0.05$ indicated statistical significance. All statistical analyses were conducted with STATA Statistical Software Release 13.1 (College Station, TX, USA).

RESULTS

Patient characteristics

We identified 676 MDS patients (median age, 75 years) and 102 CMML patients (median age, 74 years). The median follow-up was 25 months (range, 0-81 months) for the total cohort and 44 months for surviving patients. During follow-up, 54% and 71% of MDS and CMML patients died, while leukemic progression occurred in 15% and 23% of patients, respectively. Patient characteristics at diagnosis are presented in Table 1. The distribution of WHO performance status (PS) and number of comorbidities in relation to age are shown in Supplementary Figure S1 and S2, respectively. The most frequently reported comorbidity was hypertension (33%), followed by an antecedent malignancy (23%), other cardiovascular diseases (21%) and diabetes mellitus (18%). Of 178 patients with an antecedent malignancy, 31 (17%) had a hematologic malignancy.

Bone marrow morphology assessment

The following results were combined for MDS and CMML, as they did not differ significantly. A BM biopsy and aspiration were concurrently performed in 87% (679/778) of patients, while in the remaining 13%, only a BM biopsy (5%) or aspiration (8%) were performed. Almost all BM biopsies (702/720; 97%) and aspirations (710/737; 96%) were reported to be evaluable. The degree of dysplasia in erythroid (excluding ring sideroblasts), granulocytic and megakaryocytic lineages were reported in 33%, 43% and 30% of evaluable 710 BM aspirates, respectively. In contrast, ring sideroblasts were quantified in 75% of evaluable BM aspirates. Regarding the BM blast count, it was not reported in 17% of evaluable BM specimens.

Cytogenetic assessment

Cytogenetic assessments were, respectively, performed in 54% and 58% of MDS and CMML patients, and decreased progressively with older age (Figure 1). Multivariable logistic regression analysis showed that older age and ≥2 comorbidities were significantly associated with not performing cytogenetic assessments (Table 2). Cytogenetic assessment were significantly more likely performed among patients who received previous cytotoxic therapy for an antecedent malignancy and patients who were diagnosed in a university hospitals (Table 2).

Table 1. Patient characteristics at diagnosis

	MDS		CMML		Total	
Characteristic	N	(%)	N	(%)	N	(%)
Total No. of patients	676		102		778	
Male sex	417	(62)	68	(67)	485	(62)
Age, years						
Median (range)	75 (23-94)		74 (54-94)		75 (23-94)	
18-59	49	(7)	6	(6)	55	(7)
60-69	142	(21)	23	(23)	165	(21)
70-79	295	(44)	49	(48)	344	(44)
≥80	190	(28)	24	(24)	214	(28)
WHO 2008 classification						
RCUD	62	(9)				
RARS	55	(8)				
RCMD	248	(37)				
MDS with del(5q)	13	(2)				
RAEB-1	94	(14)				
RAEB-2	89	(13)				
MDS-U	8	(1)				
MDS NOS	107	(16)				
CMML-1			86	(84)		
CMML-2			16	(16)		
Hospital of diagnosis						
Non-university	626	(93)	90	(88)	716	(92)
University	50	(7)	12	(12)	62	(8)
WHO performance status						
0	285	(42)	42	(41)	327	(42)
1	333	(49)	54	(53)	387	(50)
2-4	45	(7)	5	(5)	50	(6)
Unknown	13	(2)	1	(1)	14	(2)
Median no. of comorbidities (range)	2 (0-8)		2 (0-7)		2 (0-8)	
Previous cytotoxic therapy						
No	603	(89)	95	(93)	698	(90)
Yes	73	(11)	7	(7)	80	(10)
RBC transfusion dependent[a]						
No	650	(96)	99	(97)	749	(96)
Yes	26	(4)	3	(3)	29	(4)

Abbreviations: MDS, myelodysplastic syndromes; CMML, chronic myelomonocytic leukemia; No, number; WHO, World Health Organization; RCUD, refractory cytopenia with unilineage dysplasia; RARS, anemia (RA) with ring sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia; RAEB, RA with excess blasts; MDS-U, unclassifiable MDS; NOS, not otherwise specified; RBC, red blood cell. [a]RBC transfusion dependency was defined as having ≥1 RBC transfusion every 8 weeks over a period of 4 months according to the definition set by Malcovati *et al*.[25]

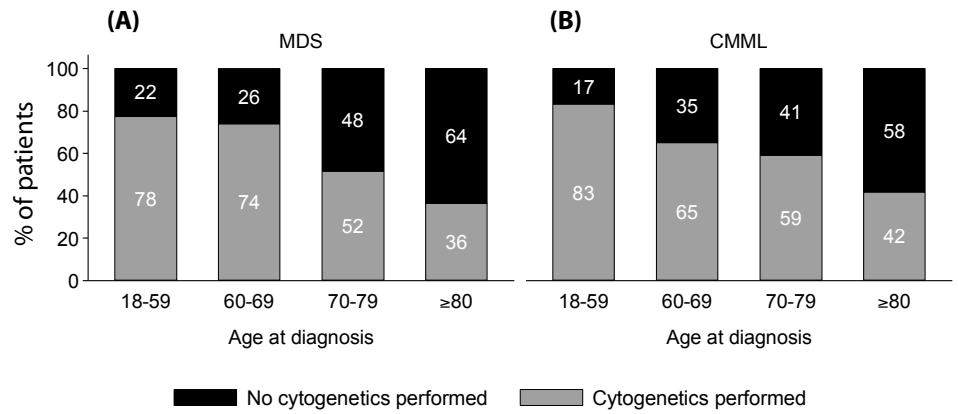

Figure 1. The performance of cytogenetic assessments at diagnosis among patients with (A) myelodysplastic syndromes (MDS) and (B) chronic myelomonocytic leukemia (CMML) according to age at diagnosis. The performance of cytogenetic assessments decreased in parallel with older age among patients with MDS (*P* for trend < 0.001) and CMML (*P* for trend = 0.037). In the overall series, karyotyped patients were significantly younger than non-karyotyped patients (median age 72 vs 77 years; *P*<0.001).

Risk assessment

The distribution of prognostic scores studied herein and their respective prognostic variables are presented in Supplementary Table S1. The IPSS, IPSS-R and CPSS could not be calculated for, respectively, 55%, 54% and 42% of patients, mainly due to unperformed cytogenetics.

The IPSS-R correlated highly to the initial IPSS (Kendall tau = 0.78; *P*<0.001; Figure 2). Further, the IPSS-R could delineate MDS patients with IPSS intermediate-1 and -2 risk scores into several IPSS-R categories (Figure 2).

OS for patients who did not receive anti-neoplastic therapy is shown in Figure 3 according to IPSS, IPSS-R, age-adjusted IPSS-R and CPSS risk groups. All prognostic scores could separate distinct risk groups, although for CPSS this was not statistically significant (log-rank *p*=0.078; Figure 3d).

Median OS and C-index estimates for all prognostic scores studied herein are presented in Table 3. The IPSS-R and the age-adjusted IPSS-R had the highest discriminatory ability according to the C-index estimate (C-index = 0.737 and 0.749, respectively) as compared to the IPSS (C-index = 0.666).

Table 2. Results of the logistic regression analyses on potential predictors associated with the decision to perform cytogenetic assessments among patients with MDS and CMML

	Univariable			Multivariable		
Independent variable	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Disease subtype						
MDS	1	(ref)				
CMML	1.09	0.68-1.77	0.712			
Sex						
Male	1	(ref)				
Female	0.97	0.73-1.30	0.846			
Age[a]	0.48	0.40-0.58	< 0.001	0.54	0.45-0.66	< 0.001
Hospital of diagnosis						
Non-university	1	(ref)		1	(ref)	
University	6.35	2.98-13.5	< 0.001	4.01	1.82-8.82	0.001
WHO performance status						
0	1	(ref)		1	(ref)	
1	0.7	0.52-0.94	0.018	0.91	0.66-1.26	0.578
2-4	0.52	0.28-0.95	0.032	0.61	0.32-1.18	0.138
Unknown	0.37	0.12-1.12	0.078	0.48	0.15-1.53	0.218
No. of comorbidities						
<2	1	(ref)		1	(ref)	
≥2	0.57	0.42-0.77	< 0.001	0.71	0.51-0.98	0.037
Previous cytotoxic therapy						
No	1	(ref)		1	(ref)	
Yes	1.85	1.13-3.03	0.014	1.70	1.00-2.87	0.049
RBC transfusion dependent[b]						
No	1	(ref)				
Yes	0.58	0.27-1.23	0.157			

Abbreviations: MDS, myelodysplastic syndromes; CMML, chronic myelomonocytic leukemia; OR, odds ratio; CI, confidence interval; WHO, World Health Organisation; No, number; RBC, red blood cell. [a]Linear with estimates of ORs for 10-year difference. [b]RBC transfusion dependency was defined as having ≥1 RBC transfusion every 8 weeks over a period of 4 months according to the definition set by Malcovati *et al*.[25]

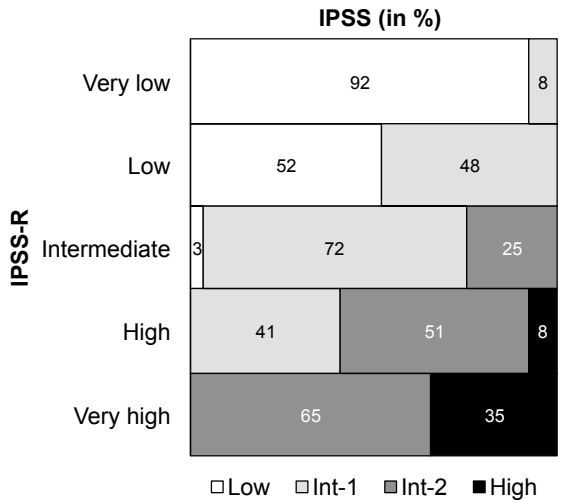

Figure 2. Comparison of the revised International Prognostic Scoring System (IPSS-R) and IPSS risk groups among patients with myelodysplastic syndromes (MDS). This analysis was limited to 302 patients with MDS who had complete data available to be stratified according to both IPSS-R and IPSS. The percentage is indicated within rows. *Abbreviations*: Int, intermediate.

Treatment

Overall treatment patterns of MDS and CMML patients according to age and IPSS risk (for MDS only) are shown in Figure 4. In the overall series, treatment of any type was started in 71% and 75% of MDS and CMML patients, while 25% and 43% of MDS and CMML patients received anti-neoplastic therapy, respectively. Percentages for treatment within university hospitals and overall trial participation were 14% and 18% and 5% and 1%, respectively.

Multivariable logistic regression analysis revealed that younger age, good PS, higher-risk disease by IPSS, and treatment in university hospitals were significantly associated with a higher odds for MDS patients to receive anti-neoplastic therapy (Table 3). MDS patients with an undetermined IPSS were significantly less likely to receive anti-neoplastic therapy compared to patients with established IPSS risk scores (Table 3). A similar multivariable logistic regression analysis for CMML was precluded due to small patient numbers within particular strata.

Table 3. Median survival (months) and C-index estimates according to several prognostic scoring systems among patients with MDS and CMML who did not received anti-neoplastic therapy

Prognostic score	N	Median OS (95% CI)		C-index[a]
IPSS				
Low	83	NR	(49.6-NR)	0.666
Intermediate-1	57	25.1	(14.7-40.1)	
Intermediate-2	18	9.3	(3.4-28.1)	
High	3	3.5	(1.9-NR)	
IPSS-R				
Very low	56	NR	NR	0.737
Low	60	29.2	(20.6-49.6)	
Intermediate	26	14.7	(9.1-45.9)	
High	11	9.7	(4.5-27.9)	
Very high	13	3.5	(1.9-15.8)	
Age-adjusted IPSS-R				
Very low	55	NR	-	0.749
Low	50	29.2	20.1-NR	
Intermediate	32	17.4	11.5-40.1	
High	16	9.7	6.0-26.9	
Very high	13	3.5	1.9-15.8	
CPSS				
Low	11	34.5	(15.4-NR)	0.634
Intermediate-1	11	27.6	(2.5-NR)	
Intermediate-2	2	3.4	(3.4-NR)	

Note: All prognostic scoring systems are calculated exclusively for patients with myelodysplastic syndromes (MDS), expect the CPSS which is exclusively calculated for patients with chronic myelomonocytic leukemia (CMML). This table shows the outcome of patients who did not received anti-neoplastic therapy (i.e. no hydroxyurea, lenalidomide, azacitidine, intensive chemotherapy and allogeneic stem cell transplantation). *Abbreviations*: CI, confidence interval; NR, not reached; IPSS, International Prognostic Scoring System; IPSS-R, revised IPSS; CPSS, CMML-specific prognostic scoring system. [a]The C-index estimates were calculated using 159 cases with complete data available to calculate all prognostic scores for MDS (i.e. not applicable for CPSS).

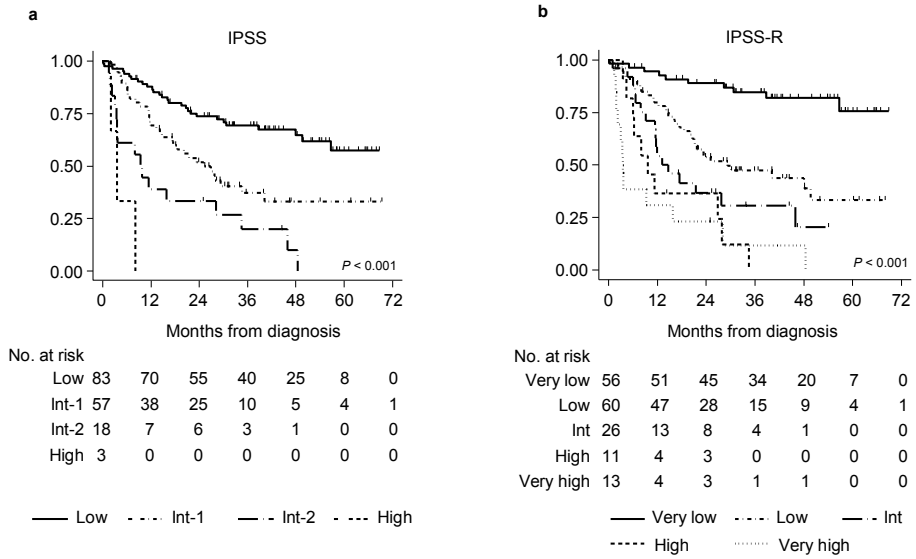

Figure 3. Overall survival among patients who did not receive anti-neoplastic therapy according to the (A) International Prognostic Scoring System (IPSS), (B) revised IPSS (IPSS-R), (C) age-adjusted IPSS-R and (D) CMML-specific Prognostic Scoring System (CPSS). All prognostic scores were calculated exclusively for patients with myelodysplastic syndromes (MDS), expect the CPSS which was exclusively calculated for patients with chronic myelomonocytic leukemia (CMML).

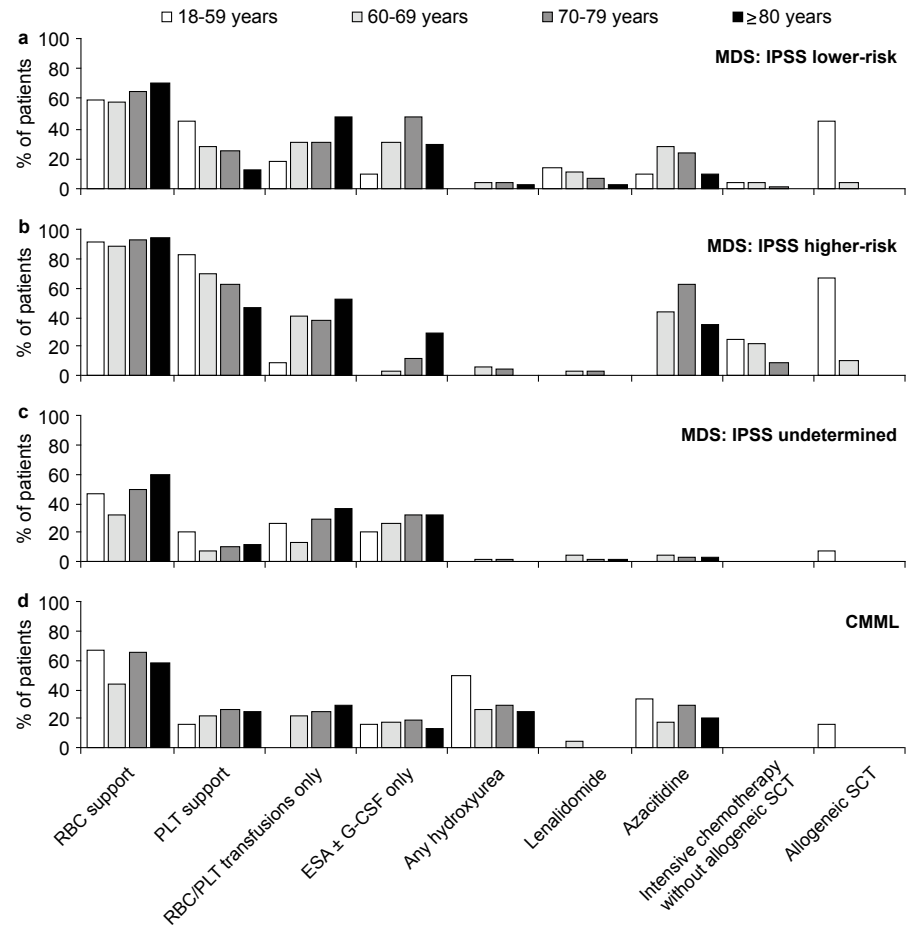

Figure 4. Overall treatment patterns of patients with myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemia (CMML) according to age at diagnosis. Panels A, B and C shows patterns of treatment among patients with MDS who have International Prognostic Scoring System (IPSS) low or intermediate-1 risk (i.e. lower-risk MDS), IPSS intermediate-2 or high risk (i.e. higher-risk MDS) and undetermined IPSS risk, respectively. The group of patients with higher-risk MDS includes 15 additional patients without a complete IPSS score who at least have an intermediate-2 IPSS at diagnosis. Panel D shows patters of treatment among patients with CMML. In the overall series, 3 and 1 of 778 patients received granulocyte-colony stimulating factor (G-CSF) monotherapy and cyclosporine, respectively (data not shown). Further, 21 (10%) of 213 patients who received erythropoietic-stimulating agents (ESA) received ESA in combination with G-CSF (data not shown). Of note, G-CSF was not provided to any patient with CMML. The absolute number and percentage of patients within a specific treatment group and age category is presented in Supplementary Table S2. *Abbreviations*: RBC, red blood cell; PLT, platelet; SCT, stem cell transplantation.

Table 4. Results of the logistic regression analyses on potential predictors associated with the application of anti-neoplastic therapy among patients with MDS

	Univariable			Multivariable		
Independent variable	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Sex						
Male	1	(ref)				
Female	0.98	0.68-1.41	0.912			
Age[a]	0.49	0.41-0.60	<0.001	0.68	0.53-0.87	0.003
WHO performance status						
0	1	(ref)		1	(ref)	
1	0.67	0.47-0.96	0.031	0.88	0.56-1.41	0.603
2-4	0.23	0.08-0.65	0.006	0.08	0.02-0.33	<0.001
Unknown	0.19	0.02-1.51	0.117	0.20	0.02-2.10	0.181
No. of comorbidities						
<2	1	(ref)		1	(ref)	
≥2	0.52	0.34-0.78	0.002	0.88	0.523-1.48	0.625
Previous cytotoxic therapy						
No	1	(ref)		1	(ref)	
Yes	1.71	1.02-2.87	0.044	1.29	0.65-2.57	0.465
RBC transfusion dependent at diagnosis[b]						
No	1	(ref)				
Yes	0.72	0.27-1.95	0.522			
Treatment at university hospital						
No	1	(ref)		1	(ref)	
Yes	7.68	4.82-12.25	<0.001	2.26	1.24-4.13	0.008
IPSS risk group at diagnosis						
Low and intermediate-1 (lower-risk)	1	(ref)		1	(ref)	
Intermediate-2 and high (higher-risk)	4.74	2.87-7.83	<0.001	5.54	3.15-9.75	<0.001
Undetermined	0.11	0.06-0.18	<0.001	0.15	0.08-0.26	<0.001

Abbreviations: MDS, myelodysplastic syndromes; OR, odds ratio; CI, confidence interval; WHO, World Health Organization; RBC, red blood cell; IPSS, International Prognostic Scoring System. [a]Linear with estimates of ORs for 10-year difference. [b]RBC transfusion dependency was defined as having ≥1 RBC transfusion every 8 weeks over a period of 4 months according to the definition set by Malcovati *et al*.[25]

DISCUSSION

MDS and CMML are disorders with heterogeneous diagnostic characteristics and clinical outcomes.[1,2] Because of this heterogeneity, clinical practice guidelines recommend that a comprehensive diagnostic approach is deemed mandatory, not only for a correct diagnosis, but also to make an accurate prediction of prognosis, which, in turn, is needed to plan well-informed risk-adapted therapy.[7,8,24] Here we report that a large proportion of MDS and CMML patients from daily practice do not undergo a diagnostic work-up containing BM dysplasia assessment, bone marrow blast enumeration and cytogenetic analysis as recommended by the clinical practice guidelines.

To our knowledge, studies evaluating the quality of BM morphology assessment in daily practice were not previously reported. Morphologic assessment of the type and degree of BM dysplasia, as well as the percentage of BM blasts is the cornerstone for accurate classification of MDS and CMML.[7,8,24] The thresholds for defining significant BM dysplasia in erythroid, granulocytic or megakaryocytic cell lineages are ≥10% according to WHO 2008 criteria.[18] In our study, approximately 95% of evaluable BM aspirates were assessed for dysplasia. However, the degree of dysplasia in erythroid, granulocytic or megakaryocytic cell lineages was not reported in most cases. Further, the blasts were not counted in 17% of evaluable BM specimens. Altogether, a careful morphologic assessment of the BM, along with proper documentation of morphologic findings, are essential to facilitate an accurate classification of MDS and CMML.

The karyotype is well-established as having strong prognostic impact in MDS and CMML and is therefore incorporated in prognostic scoring systems such as the IPSS and the IPSS-R.[19-21,25-29] Established in 1997, risk assessment according to the IPSS is still the cornerstone for prognostication and planning risk-adapted therapy in MDS as recently highlighted by the MDS work package of the ELN.[7] Despite the importance of cytogenetic assessments, they were not performed in almost half of all patients in our study, especially among the elderly. The lack of information on karyotype prevented accurate prognostication in these patients. The choice of the physician to omit cytogenetic assessment may be related to several factors such as advanced age and higher prevalence of comorbidities as shown by multivariable logistic regression analysis in our study (Table 2). Although some patients might not be eligible for a particular treatment due to older age and/or specific comorbid conditions, accurate prognostication is important to accurately counsel patients about their life expectancy. What is more is that the karyotype is also important for classification, because specific cytogenetic aberrancies are diagnostic for particular MDS subtypes, namely MDS with an isolated del(5q) and MDS unclassifiable. It is thus possible that MDS with an isolated del(5q) might be underdiagnosed by the physician, as the proportion of that particular subtype in our registry was somewhat

lower than reported in large clinical series where cytogenetic analysis is commonly performed.[19,28-30] Although MDS with an isolated del(5q) is rare, identification of this specific subtype has enormous implications for treatment decision-making, as lenalidomide is approved since 2013 by the European Medicines Agency for that particular subtype. Morphologically, MDS with an isolated del(5q) may be recognized by hypolobulated megakaryocytes. This specific feature may prompt the physician to perform cytogenetic analysis to establish (or exclude) the diagnosis of that particular subtype.

The development and subsequent external validation of prognostic scoring systems for MDS and CMML are typically based on patient series from centers of excellence.[20,21,25,27,29,31-35] Their prognostic value should therefore be extrapolated with caution to patients from general hospitals. To address this issue, we showed in our population-based study that all commonly used prognostic scores studied herein had discriminative ability in a cohort of untreated MDS and CMML patients, especially the IPSS-R. However, although somewhat limited by modest patient numbers, median OS of particular risk groups were inferior than those reported in the original reports of the IPSS[19] and the IPSS-R.[20] This might be explained by the older age and higher prevalence of comorbidities among these patients in our study who reflect the MDS population at large. Therefore, comorbidity should be integrated into risk assessment tools, especially in the IPSS-R which also can be adjusted for age.[34] Furthermore, we confirmed that the IPSS-R could more precisely delineate MDS patients with IPSS intermediate-1 and -2 risk scores into several IPSS-R categories, which was in accordance with the original article of the IPSS-R[20] and a recent validation study performed in a single tertiary referral center.[34] For example, in our study, 41% of patients within the IPSS-R high category had IPSS intermediate-1 scores, a category considered as lower-risk by the IPSS. Clearly, such finding may have implications for treatment-decision making when applied prospectively.

As expected, and confirmed in our study, younger age, good PS, high-risk disease by IPSS and treatment within university hospitals were significantly associated with higher odds of receiving anti-neoplastic therapy in MDS. Although the number of comorbidities was not a determinant for receiving anti-neoplastic therapy, specific types of comorbidities might still be associated with the choice to refrain from anti-neoplastic therapy to prevent treatment-related mortality and morbidity. Further, we showed that MDS patients with an undetermined IPSS were significantly more likely to receive supportive care modalities than lower-risk MDS patients. An undetermined IPSS results from incomplete prognostication, which, in turn, might lead to suboptimal treatment-decision making, as evidence- and consensus-based therapeutic guidelines recommend that treatment decisions should be guided by IPSS risk.[7,24] In some instances, patients with established IPSS scores did not receive a treatment modality recommended for their particular risk group.[7] For example, some patients with lower-risk MDS received azacitidine, whereas some patients with higher-risk MDS received erythropoiesis-stimulating agents.

We showed that less than 5% of MDS and CMML patients in our study were included in clinical trials, which was much lower than the overall trial participation rates in acute leukemias as we reported previously.[36,37] To date, no other studies reported on trial participation in MDS and CMML. The low trial participation in MDS and CMML may be explained by the scarcity of clinical trials in these disorders. In addition, eligibility criteria for current clinical trials might be too stringent, thereby preventing broad patient enrollement.

The key strength of the PHAROS MDS registry relative to other specialized MDS and CMML registries is that it relies on the nationwide NCR for case notification, thereby it truly reflects the actual clinical practice within a well-defined area. As such, we were able to provide real-world data on diagnosis and treatment of MDS and CMML patients in daily practice, which revealed that the quality of care to these patients can be improved. To our knowledge, the PHAROS MDS registry is the first specialized population-based registry in MDS and CMML that has its roots in a population-based cancer registry (that is, the NCR). Our registry therefore provides data complementary to the NCR.[4,5] Although we certainly appreciate the few available specialized population-based registries in MDS, they are prone to selection and/or referral biases.[11-15] Accordingly, their study population might perhaps not reflect the actual clinical practice. For example, the recently established EU-MDS registry for lower-risk MDS is based on registration of patients from 118 participating centers across 14 European countries.[13] It is unclear what the degree of center and subsequent patient selection was in that registry. Similar biases exist for the recently established specialized MDS registries in Poland[14] and Minnesota, United States.[15]

In conclusion, we show that most MDS and CMML patients undergo a comprehensive and proper diagnostic work-up. However, cytogenetic assessments were not performed in almost half of all patients. Consequently, an accurate risk assessment could not be made in these patients, which, in turn, might result in inappropriate treatment-decision making. Population-based registries with a good coverage of a defined population can be useful instruments to characterize patient populations not included in clinical trials. Further, they can be used to assess guideline adherence and may be part of guideline development.

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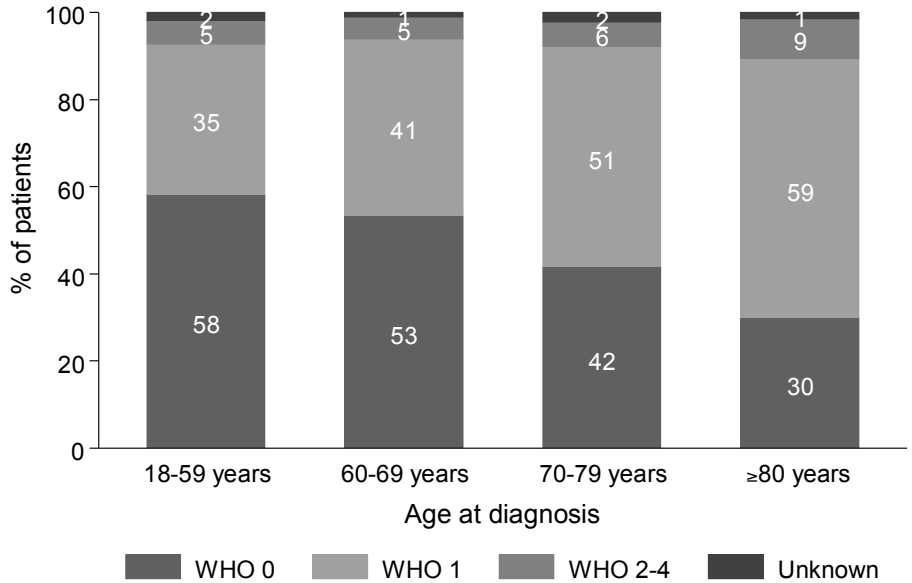
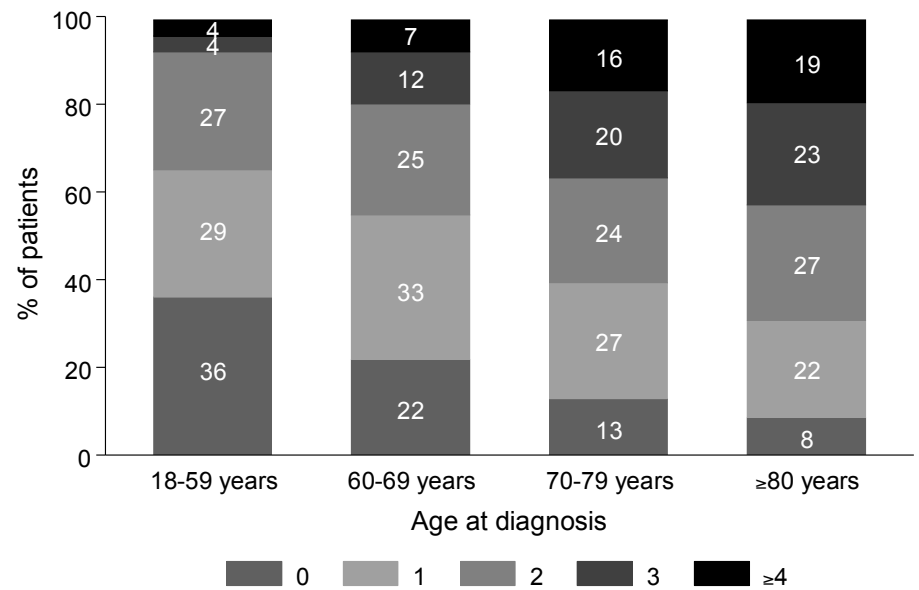
SUPPLEMENTARY FIGURES



Supplementary Figure S1. WHO performance status (PS) among patients with myelodysplastic syndromes and chronic myelomonocytic leukemia according to age at diagnosis. The proportion of patients with WHO PS of 0 decreased in parallel with older age (*P* for trend < 0.001), while the proportion of patients with WHO PS of 1 increased in parallel with older age (*P* for trend < 0.001). Similarly, the proportion of patients with WHO PS of 2-4 increased in parallel with older age; however, this increase was not statistically significant (*P* for trend = 0.097). *Abbreviation*: WHO, World Health Organization.



Supplementary Figure S2. Number of comorbidities at diagnosis among patients with myelodysplastic syndromes and chronic myelomonocytic leukemia according to age at diagnosis. The proportion of patients with no or 1 comorbidity decreased in parallel with older age (*P* for trend < 0.001 and *P* for trend = 0.038, respectively), while the proportion of patients with 3 or ≥4 comorbidities increased in parallel with older age (*P* for trend < 0.001 for both). An increasing or decreasing linear trend was not observed for patients with 2 comorbidities (*P* for trend = 0.967).

Supplementary Table S1. Prognostic scores in MDS and CMML and their respective prognostic variables

IPSS	N	% of total	(% of total without unknown)
Karyotype			
Good	248	37	(68)
Intermediate	54	8	(15)
Poor	62	9	(17)
Unknown	312	46	
BM blast, %			
<5	370	55	(68)
5-10	113	17	(21)
11-20	63	9	(12)
Unknown	130	19	
No. of cytopenias			
0-1	401	59	(63)
2-3	240	36	(37)
Unknown	35	5	
Risk groups			
Low	100	15	(33)
Intermediate-1	111	16	(36)
Intermediate-2	73	11	(24)
High	21	3	(7)
Undetermined	371	55	

IPSS-R	N	% of total	(% of total without unknown)
Karyotype			
Very good	24	4	(7)
Good	227	34	(62)
Intermediate	52	8	(14)
Poor	26	4	(7)
Very poor	35	5	(10)
Unknown	312	46	
BM blast, %			
≤2	271	40	(50)
>2-<5	99	15	(18)
5-10	112	17	(21)
>10	64	9	(12)
Unknown	130	19	
Hemoglobin, g/dl			
≥10	343	51	
8-<10	212	31	
<8	121	18	
Platelets, 10^9/l			
≥100	429	63	(64)
50-<100	141	21	(21)
<50	103	15	(15)
Unknown	3	0	
ANC, 10^9/l			
≥0.8	517	76	(84)
<0.8	99	15	(16)
Unknown	60	9	
Risk groups			
Very low	63	9	(20)
Low	86	13	(28)
Intermediate	64	9	(21)
High	49	7	(16)
Very high	49	7	(16)
Undetermined	365	54	

Age-adjusted IPSS-R	N	% of total	(% of total without unknown)
Risk groups			
Very low	62	9	(20)
Low	73	11	(23)
Intermediate	68	10	(22)
High	54	8	(17)
Very high	54	8	(17)
Undetermined	365	54	

CPSS	N	% of total	(% of total without unknown)
Karyotype			
Low	44	43	(75)
Intermediate	6	6	(10)
High	9	9	(15)
Unknown	43	42	
WHO subtype			
CMML-1	86	84	
CMML-2	16	16	
FAB subtype			
CMML-MD	45	44	
CMML-MP	57	56	
Transfusion requirement[b]			
No	95	93	
Regular	7	7	
Risk groups			
Low	16	16	(27)
Intermediate-1	23	23	(39)
Intermediate-2	20	20	(34)
High	0	0	(0)
Undetermined	43	42	

Note: The IPSS, IPSS-R and age-adjusted IPSS-R are based on 676 patients with myelodysplastic syndromes (MDS), while the CPSS is based on 102 patients with chronic myelomonocytic leukemia (CMML). *Abbreviations*: IPSS, International Prognostic Scoring System; BM, bone marrow; No, number; RA, refractory anemia; RARS, RA with ringsideroblasts; RCMD, refractory cytopenia with multilineage dysplasia (RCMD); RAEB, RA with excess blasts; BM, bone marrow; IPSS-R, revised IPSS; ANC, absolute neutrophil count; CPSS, CMML-specific Prognostic Scoring System; FAB, French-American-British; MD, myelodysplastic; MP, myeloproliferative. [a]Includes patients with the diagnosis of unclassifiable MDS (3%) and MDS, not otherwise specified (17%). [b]Transfusion requirement was defined as having ≥1 red blood cell transfusion every 8 weeks over a period of 4 months according to the definition set by Malcovati *et al*.[25]

Supplementary Table S2. Overall treatment patterns of patients with MDS and CMML according to age at diagnosis

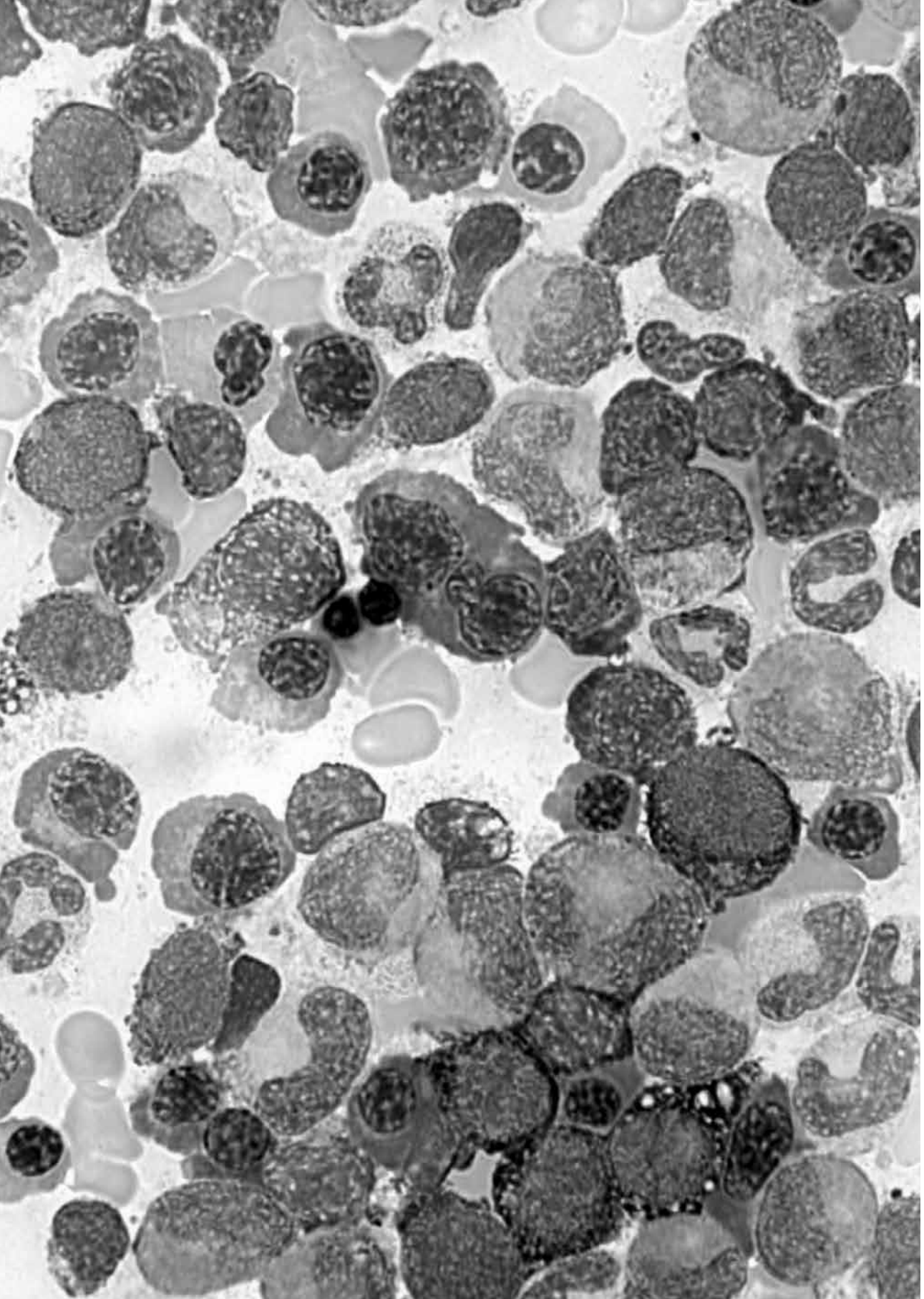
MDS: IPSS lower-risk[a]	Age at diagnosis, years (patient numbers)																			
	18-59 (n = 22)				60-69 (n = 54)				70-79 (n = 95)				≥80 (n = 40)				Total (n = 211)			
	No		Yes		No		Yes		No		Yes		No		Yes		No		Yes	
Treatment	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
RBC support	9	(41)	13	(59)	23	(43)	31	(57)	34	(36)	61	(64)	12	(30)	28	(70)	78	(37)	133	(63)
PLT support	12	(55)	10	(45)	39	(72)	15	(28)	71	(75)	24	(25)	35	(88)	5	(13)	157	(74)	54	(26)
RBC/PLT transfusions only	18	(82)	4	(18)	37	(69)	17	(31)	66	(69)	29	(31)	21	(53)	19	(48)	142	(67)	69	(33)
ESA ± G-CSF only	20	(91)	2	(9)	37	(69)	17	(31)	50	(53)	45	(47)	28	(70)	12	(30)	135	(64)	76	(36)
Any hydroxyurea	22	(100)	0	(0)	52	(96)	2	(4)	91	(96)	4	(4)	39	(98)	1	(3)	204	(97)	7	(3)
Lenalidomide	19	(86)	3	(14)	48	(89)	6	(11)	89	(94)	6	(6)	39	(98)	1	(3)	195	(92)	16	(8)
Azacitidine	20	(91)	2	(9)	39	(72)	15	(28)	72	(76)	23	(24)	36	(90)	4	(10)	167	(79)	44	(21)
Intensive chemotherapy[b]	21	(95)	1	(5)	52	(96)	2	(4)	94	(99)	1	(1)	40	(100)	0	(0)	207	(98)	4	(2)
Allogeneic SCT	12	(55)	10	(45)	52	(96)	2	(4)	95	(100)	0	(0)	40	(100)	0	(0)	199	(94)	12	(6)

MDS: IPSS higher-risk[c]	Age at diagnosis, years (patient numbers)																			
	18-59 (n = 12)				60-69 (n = 37)				70-79 (n = 43)				≥80 (n = 17)				Total (n = 109)			
	No		Yes		No		Yes		No		Yes		No		Yes		No		Yes	
Treatment	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
RBC support	1	(8)	11	(92)	4	(11)	33	(89)	3	(7)	40	(93)	1	(6)	16	(94)	9	(8)	100	(92)
PLT support	2	(17)	10	(83)	11	(30)	26	(70)	16	(37)	27	(63)	9	(53)	8	(47)	38	(35)	71	(65)
RBC/PLT transfusions only	11	(92)	1	(8)	22	(59)	15	(41)	27	(63)	16	(37)	8	(47)	9	(53)	68	(62)	41	(38)
ESA ± G-CSF only	12	(100)	0	(0)	36	(97)	1	(3)	38	(88)	5	(12)	12	(71)	5	(29)	98	(90)	11	(10)
Any hydroxyurea	12	(100)	0	(0)	35	(95)	2	(5)	41	(95)	2	(5)	17	(100)	0	(0)	105	(96)	4	(4)
Lenalidomide	12	(100)	0	(0)	36	(97)	1	(3)	42	(98)	1	(2)	17	(100)	0	(0)	107	(98)	2	(2)
Azacitidine	12	(100)	0	(0)	21	(57)	16	(43)	16	(37)	27	(63)	11	(65)	6	(35)	60	(55)	49	(45)
Intensive chemotherapy[b]	9	(75)	3	(25)	29	(78)	8	(22)	39	(91)	4	(9)	17	(100)	0	(0)	94	(86)	15	(14)
Allogeneic SCT	4	(33)	8	(67)	33	(89)	4	(11)	43	(100)	0	(0)	17	(100)	0	(0)	97	(89)	12	(11)

MDS: IPSS undetermined	Age at diagnosis, years (patient numbers)																			
	18-59 (n = 15)				60-69 (n = 51)				70-79 (n = 157)				≥80 (n = 133)				Total (n = 356)			
	No		Yes		No		Yes		No		Yes		No		Yes		No		Yes	
Treatment	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
RBC support	8	(53)	7	(47)	35	(69)	16	(31)	79	(50)	78	(50)	53	(40)	80	(60)	175	(49)	181	(51)
PLT support	12	(80)	3	(20)	47	(92)	4	(8)	140	(89)	17	(11)	118	(89)	15	(11)	317	(89)	39	(11)
RBC/PLT transfusions only	11	(73)	4	(27)	44	(86)	7	(14)	112	(71)	45	(29)	84	(63)	49	(37)	251	(71)	105	(29)
ESA ± G-CSF only	12	(80)	3	(20)	38	(75)	13	(25)	106	(68)	51	(32)	91	(68)	42	(32)	247	(69)	109	(31)
Any hydroxyurea	15	(100)	0	(0)	50	(98)	1	(2)	155	(99)	2	(1)	133	(100)	0	(0)	353	(99)	3	(1)
Lenalidomide	15	(100)	0	(0)	49	(96)	2	(4)	155	(99)	2	(1)	132	(99)	1	(1)	351	(99)	5	(1)
Azacitidine	15	(100)	0	(0)	49	(96)	2	(4)	152	(97)	5	(3)	130	(98)	3	(2)	346	(97)	10	(3)
Intensive chemotherapy[b]	15	(100)	0	(0)	51	(100)	0	(0)	157	(100)	0	(0)	133	(100)	0	(0)	356	(100)	0	(0)
Allogeneic SCT	14	(93)	1	(7)	51	(100)	0	(0)	157	(100)	0	(0)	133	(100)	0	(0)	355	(100)	1	(0)

CMML	Age at diagnosis, years (patient numbers)																			
	18-59 (n = 6)				60-69 (n = 23)				70-79 (n = 49)				≥80 (n = 24)				Total (n = 102)			
	No		Yes		No		Yes		No		Yes		No		Yes		No		Yes	
Treatment	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
RBC support	2	(33)	4	(67)	13	(57)	10	(43)	17	(35)	32	(65)	10	(42)	14	(58)	42	(20)	60	(28)
PLT support	5	(83)	1	(17)	18	(78)	5	(22)	36	(73)	13	(27)	18	(75)	6	(25)	77	(36)	25	(12)
RBC/PLT transfusions only	6	(100)	0	(0)	18	(78)	5	(22)	37	(76)	12	(24)	17	(71)	7	(29)	78	(37)	24	(11)
ESA ± G-CSF only	5	(83)	1	(17)	19	(83)	4	(17)	40	(82)	9	(18)	21	(88)	3	(13)	85	(40)	17	(8)
Any hydroxyurea	3	(50)	3	(50)	17	(74)	6	(26)	35	(71)	14	(29)	18	(75)	6	(25)	73	(35)	29	(14)
Lenalidomide	6	(100)	0	(0)	22	(96)	1	(4)	49	(100)	0	(0)	24	(100)	0	(0)	101	(48)	1	(0)
Azacitidine	4	(67)	2	(33)	19	(83)	4	(17)	35	(71)	14	(29)	19	(79)	5	(21)	77	(36)	25	(12)
Intensive chemotherapy[b]	6	(100)	0	(0)	23	(100)	0	(0)	49	(100)	0	(0)	24	(100)	0	(0)	102	(48)	0	(0)
Allogeneic SCT	5	(83)	1	(17)	23	(100)	0	(0)	49	(100)	0	(0)	24	(100)	0	(0)	101	(48)	1	(0)

Abbreviations: MDS, myelodysplastic syndromes; CMML, chronic myelomonocytic leukemia; IPSS, International Prognostic Scoring System; RBC, red blood cell; PLT, platelet; ESA, erythropoietic-stimulating agent; G-CSF, granulocyte-colony stimulating factor; SCT, stem cell transplantation. [a]Patients who have IPSS low or intermediate-1 risk MDS were categorized as lower-risk MDS. [b]Does not include patients who proceeded to an allogeneic SCT. [c]Patients who have IPSS intermediate-2 or high risk MDS were categorized as higher-risk MDS. The group of patients with higher-risk MDS also includes 15 additional patients without a complete IPSS score who at least have an intermediate-2 IPSS at diagnosis.



Effectiveness of azacitidine for the treatment of higher-risk myelodysplastic syndromes in daily practice: results from the Dutch population-based PHAROS MDS registry

7

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We read with interest the recent article by Bernal *et al*.[1] on the effectiveness of azacitidine for the treatment of higher-risk myelodysplastic syndromes (HR-MDS), based on registration of patients by hematologists in selected hospitals in Spain. That study provided valuable findings complementary to that obtained from clinical trials, which generally includes selected patient populations. The main finding of their study was that there was no beneficial effect of azacitidine. Their patient population included a heterogeneous group of patients with HR-MDS, chronic myelomonocytic leukemia and acute myeloid leukemia (AML) with 20%-30% blasts, which may limit the generalizability of the study results to a population with exclusively HR-MDS.

In order to complement and extend their observations in a more homogenous population, including all patients within a well-defined area, we conducted a retrospective, population-based cohort study to assess the effectiveness of azacitidine compared with best supportive care (BSC) only and intensive chemotherapy (IC) for the treatment of transplant-ineligible patients with exclusively HR-MDS in the Netherlands.

We selected 121 (azacitidine, *n*=66; BSC only, *n*=37; and IC, *n*=18) over 18-year-old transplant-ineligible HR-MDS patients diagnosed between 2008-2011 from the Dutch **P**opulation-based **HA**ematological **R**egistry for **O**bservational **S**tudies (PHAROS) in MDS (see Supplementary Figure S1 for patient flow and Supplementary Table S1 for patient characteristics). We exclusively selected World Health Organization-defined MDS patients with intermediate-2 or high-risk on the International Prognostic Scoring System, which is an approved indication for treatment with azacitidine. Central review of diagnostic specimens was not possible due to the retrospective nature of this study. The PHAROS MDS registry is a true population-based registry, which relies on the nationwide Netherlands Cancer Registry (NCR) for case ascertainment; its coverage is therefore identical to the NCR (see Supplementary Figure S2 for study design). The validity and completeness of the NCR were previously reported.[2-4] Details about the registries and treatment definitions are provided in the Supplementary Information. The study was approved by the Ethics Committee of the Erasmus University Medical Center.

Azacitidine and IC were, respectively, given for a median (range) of 8.5 (1-26) and 2 (1-3) cycles, and BSC only for a median of 4.2 (0-30.5) months. After a median (range) follow-up of 14.6 (0.3-68.9) months, median overall survival (OS) was 16.9, 7.3 and 14.3 months for patients receiving azacitidine, BSC only and IC, respectively (Figure 1a-b). By multivariate Cox regression analysis, treatment with azacitidine relative to BSC only (hazard ratio [HR]=0.61; *P*=0.039), and good- (*P*=0.009) and intermediate-risk cytogenetics (*P*=0.003) were significantly associated with better survival, whereas hemoglobin <10 g/dL (*P*=0.008) exhibited the opposite association (Supplementary Table S2). Although survival was similar with either azacitidine or IC (Figure 1b; HR=0.88; *P*=0.699; Supplementary Table S2), patients receiving IC spend substantial more days hospitalized than azacitidine-treated patients (median days, 71 vs 2.5; *P*<0.001; Table 1). Of note, in line with previous reports,[1,5] patients with -7/del(7q) abnormalities seem to benefit significantly from azacitidine compared with BSC only and IC (median OS 21.4 vs 3.9 months; *P*=0.019; Supplementary Figure S3).

The proportion of patients achieving hematological remission based on International Working Group 2006 criteria for MDS was 30%, 0% and 67% for patients receiving azacitidine, BSC only and IC, respectively (Table 1). The corresponding estimates for hematological improvement were 39%, 0% and 39%, respectively (Table 1). As for leukemic transformation in the overall series, the corresponding estimates were 51%, 35% and 39%, respectively (*P*=0.231). The proportion of relapse was similar between patients receiving azacitidine or IC (Table 1).

The median (range) time to best response with azacitidine was 5 (1-12) cycles (Supplementary Table S3). Patients who responded to azacitidine received a median (range) of 13.5 (3-26) cycles, whereas non-responders received 5 (1-18) cycles (Supplementary Table S3). Median OS was significantly higher in responders compared with non-responders (*P*=0.002; Figure 1c-d). Survival was similar between non-responding azacitidine-treated patients and patients who received BSC only (*P*=0.682; Figure 1d).

In contrast to our study, the study by Bernal *et al*. could not demonstrate any beneficial effect of azacitidine.[1] Several possibilities can be considered to explain the differences. First, our patients received an increased number of azacitidine cycles than Spanish patients (median, 8.5 vs 6). As demonstrated in the AZA-001 trial,[5,6] long-term treatment with azacitidine (that is, ≥6 treatment cycles) seems necessary to reach and maintain clinical benefit. Interestingly, our azacitidine-treated patients received a similar number of treatment cycles as patients in the AZA-001 trial[5] (median, 8.5 vs 9); still, our azacitidine-treated patients (85% managed in non-university hospitals) fared much worse (median OS, 16.9 vs 24.5 months), which might indicate patient selection in clinical trials. For example, azacitidine-treated patients in our study have comparatively unfavorable features than azacitidine-treated patients in the AZA-001 trial, such as more frequent poor-risk cytogenetics (44% vs 28%) and therapy-related MDS (18% vs 0%).[5] The incidence of these higher-risk features was similar between our study and the Spanish study.[1] Secondly, although information on response was lacking in the Spanish study, we show that patients who achieved a response to azacitidine seems to have better survival than non-responders.[1] As shown for azacitidine-treated patients in the AZA-001 trial,[7] achievement of a response seems to translate into a survival benefit relative to non-responders, although a response is not necessarily a prerequisite for clinical benefit. Together, our population-based data suggests that azacitidine might be a suitable treatment approach for elderly HR-MDS patients. Nevertheless, survival curves of azacitidine and BSC only converge at approximately 2.5 years, which is not unexpected since azacitidine is a non-curative disease-modifying agent.

In agreement with the Spanish study, outcome with either azacitidine or IC was similar.[1] Such observation was recently noted among elderly AML patients in the AZA-AML-001 trial.[8] In addition, we show that patients receiving IC spend substantial more time hospitalized than azacitidine-treated patients. Collectively, azacitidine might be an alternative treatment approach for HR-MDS patients who are likely to tolerate and benefit from IC, but refrain from it and its related long-term hospitalization.

Well-established population-based studies with representative patient populations are useful to assess whether findings from clinical trials translate into benefits for patients in daily practice.

AKNOWLEDGEMENTS

The **P**opulation-based **HA**ematological **R**egistry for **O**bservational **S**tudies (PHAROS) is an initiative of the Dutch-Belgian Hemato-Oncology Group (HOVON), the institute of Medical Technology Assessment (iMTA/BMG) at the Erasmus University Rotterdam and the Netherlands Comprehensive Cancer Organisation (IKNL). We are grateful to all participating centers, hematologist, research nurses and data managers for their contributions and efforts, which allowed for additional data collection. We especially thank Ms. Hind al Attabi and Dr. Liyan Qiu for the dedicated data collection. This work was financially supported by grants from The Netherlands Organization for Health Research and Development (ZonMw; #152001007).

Table 1. Treatment outcomes of patients with higher-risk MDS by treatment group

	Treatment group						*P* value[a]	
	Azacitidine (n = 66)		BSC only (n = 37)		IC (n = 18)		Azacitidine vs BSC only	Azacitidine vs IC
	n	(%)	n	(%)	n	(%)		
Hospitalization, days								
Median (range)	2.5 (0-53)		4 (0-86)		71 (3-150)		0.989	< 0.001
Hematological response								
Any hematological remission[b]	20	(30)	0		12	(67)	< 0.001	0.007
Complete remission (CR)	8	(12)	0		7	(39)	-	-
Partial remission (PR)	2	(3)	0		0		-	-
Marrow CR (mCR)	10	(15)	0		5	(28)	-	-
Stable disease	8	(12)	0		0		-	-
Progressive disease (PD)	20	(30)	11	(30)	3	(17)	-	-
Not evaluated[c]	18	(27)	26	(70)	3	(17)	-	-
Hematological improvement (HI)[d]								
Any hematological improvement	26	(39)	0		7	(39)	< 0.001	1
Erythroid response	22	(33)	0		6	(33)	-	-
Platelet response	22	(33)	0		5	(28)	-	-
Neutrophil response	12	(18)	0		2	(11)	-	-
Overall response[e]	32	(48)	0		12	(67)	< 0.001	0.194
Relapse after CR, PR or mCR[f]	12	(60)	0		6	(50)	-	0.718
Relapse after HI[g]	17	(65)	0		4	(57)	-	0.686

Abbreviations: BSC, best supportive care; IC, intensive chemotherapy. [a] Characteristics of patients were compared with the Fisher's exact test for categorical variables, and the Kruskal–Wallis test for continuous variables. $P<0.05$ indicated statistical significant differences. [b] Any hematological remission includes CR, PR or mCR. [c] In this patient subset, a bone marrow assessment was not performed. The decision to perform a bone marrow assessment was always at the discretion of the treating physician. [d] The proportion of patients achieving a hematological improvement was calculated for the entire patient group (that is, the intention to treat population). [e] Overall response includes patients who achieved CR, PR, mCR or HI with or without SD. [f] The proportion of relapse after CR, PR or mCR was calculated based on the number of patients who achieved a hematological remission ($n = 20$). [g] The proportion of relapse after HI was calculated based on the number of patients who achieved a hematological improvement ($n = 26$). Hematological response and improvement were assessed according to the International Working Group 2006 criteria for MDS.

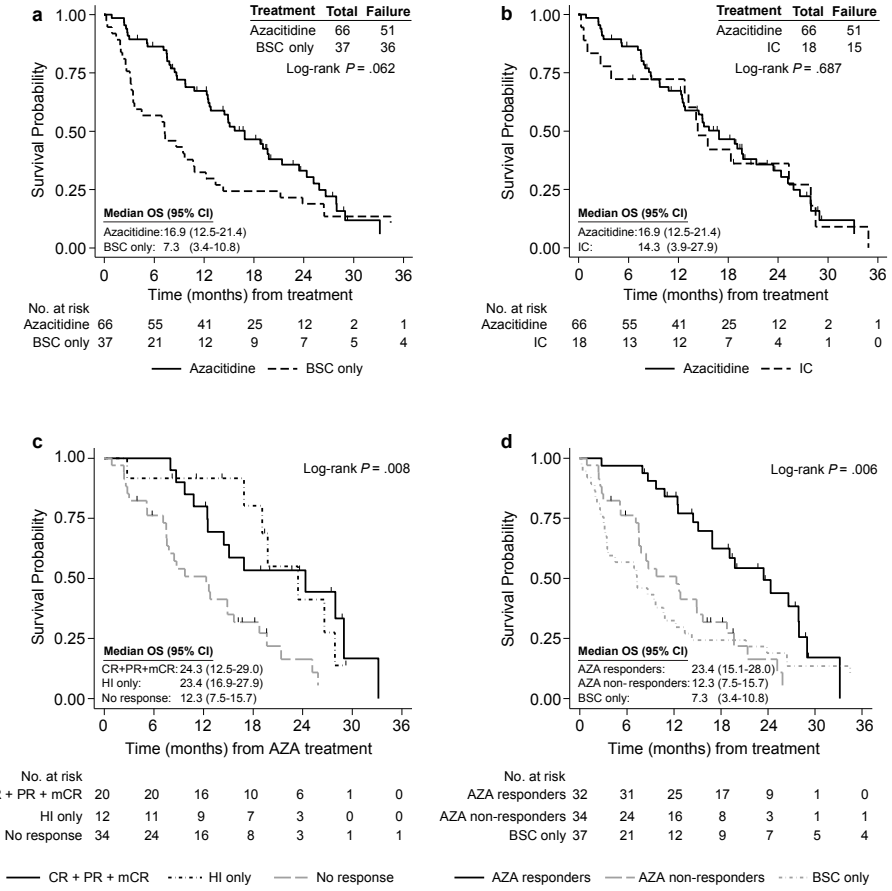

Figure 1. Overall survival (OS) of patients with higher-risk myelodysplastic syndromes (HR-MDS) treated with azacitidine compared to patients with HR-MDS receiving **(a)** best supportive care (BSC) only or **(b)** intensive chemotherapy (IC). **(c)** OS of patients with HR-MDS treated with azacitidine according to the type of response **(d)** compared to patients with HR-MDS receiving BSC only. In Figure 1d, patients who responded to azacitidine were grouped as those who achieved a complete remission (CR), partial remission (PR), marrow CR (mCR) or hematologic improvement (HI) with or without stable disease (SD). In that same Figure, as well as in Figure 1c, non-responders were defined as patients without a bone marrow evaluation and lacking a HI, SD without HI, or progressive disease. Hematological remission and improvement were based on International Working Group 2006 criteria for MDS. OS was measured with the Kaplan-Meier method as the time from treatment to death or last follow-up, and compared with the log-rank test. *Abbreviations*: CI, confidence interval; AZA, azacitidine.

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SUPPLEMENTARY METHODS

Population-based registries

Since 1989, all newly diagnosed malignancies in the Netherlands are recorded in the nationwide population-based Netherlands Cancer Registry (NCR), which is maintained and hosted by the Netherlands Comprehensive Cancer Organisation. The overall coverage of the NCR is estimated at more than 95%.[1] The NCR predominantly receives notification of all newly diagnosed malignancies in the Netherlands from the Nationwide Network of Histopathology and Cytopathology and the National Hospital Discharge Registry. A minimal dataset containing basic information on demographic (for example, gender and dates of birth and diagnosis) and clinical characteristics (for example, disease subtype and initial treatment) are collected by trained registrars of the NCR via retrospective medical records review according to standardized procedures set by the NCR, which follows the recommendations of the World Health Organization (WHO) and the International Association of Cancer Registries (IACR). The primary role of the NCR is to provide information on incidence, primary treatment and survival of all malignancies in the Netherlands. This information was previously reported by our group for myelodysplastic syndromes (MDS).[2] Although this information is crucial for national cancer control activities, they are insufficient to address more specific questions regarding the delivery of care to patients with MDS, which requires additional, more detailed data. Therefore, the Dutch **P**opulation-based **HA**ematological **R**egistry for **O**bservational **S**tudies (PHAROS) in MDS—the PHAROS MDS registry—was established to document additional, more detailed data on classification, prognostication, and various patient- and treatment-related characteristics next to the minimal dataset of the NCR (see Supplementary Figure S2 for study design). While the NCR entirely covers the Netherlands (16.3 million people), the PHAROS MDS registry essentially covers the west part of the Netherlands with 6.3 million people (almost 40% of the Dutch population), and 3 university and 27 non-university hospitals. The PHAROS MDS registry is a joint initiative of the Dutch-Belgian Hemato-Oncology Group (HOVON), the institute of Medical Technology Assessment at the Erasmus University Rotterdam and the Netherlands Comprehensive Cancer Organisation.

Treatment

According to treatment guidelines for higher-risk MDS (HR-MDS) set by HOVON, the recommended dosage of azacitidine is 75 mg/m^2 per day during 7 days every 28 days, for at least 6 cycles. These recommendations followed European Medicines Agency approval for use of azacitidine in HR-MDS. Sixty-eight percent of azacitidine-treated patients started with the recommended 7 day dosing (Supplementary Table S1). This schedule also includes 7 days non-consecutive dosing with a 2-day break (that is, a 5-2-2 schedule).

Dose reductions, delays in treatment cycles, and treatment continuation or discontinuation were all at the discretion of the treating physician. Intensive chemotherapy for HR-MDS always includes induction with cytarabine for 7 days and either idarubicin or daunorubicin for 3 days according to acute myeloid leukemia treatment protocols of HOVON. Best supportive care consists of watchful waiting (including treatment with antibiotics), red blood cell- and/or platelet transfusions or treatment with erythropoiesis-stimulating agents (ESAs) whether or not in combination with transfusions. Of note, low-dose cytarabine is not routinely used for the treatment of MDS in the Netherlands.

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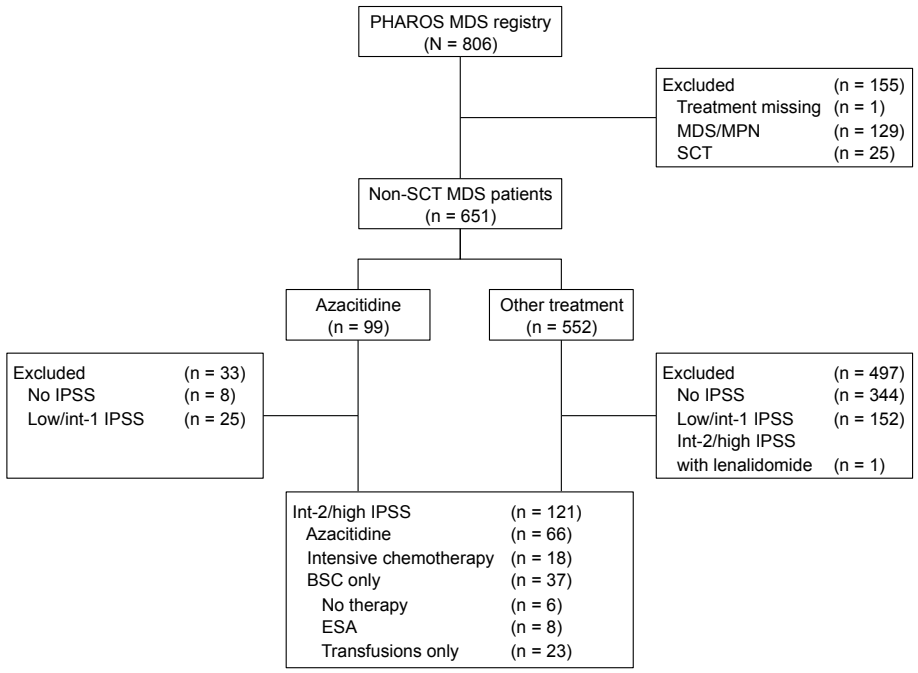
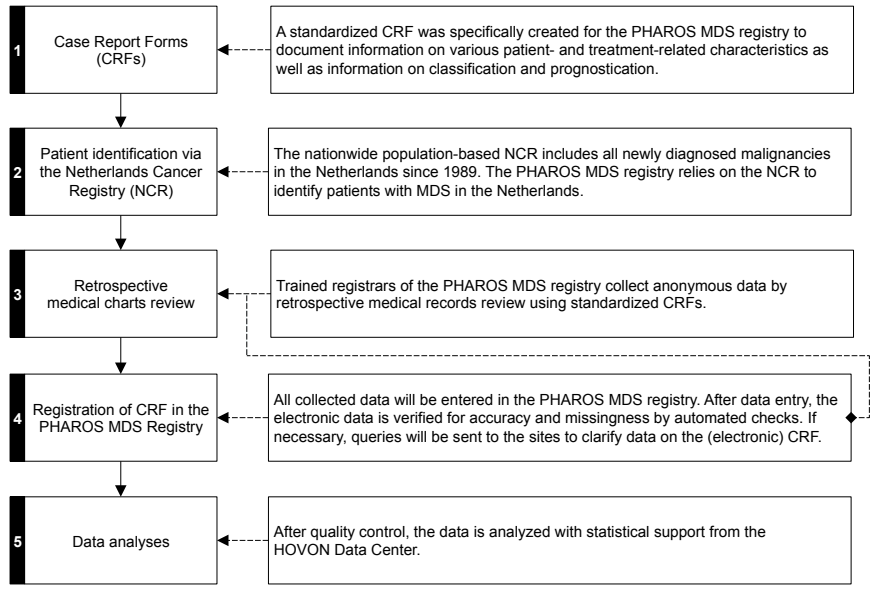
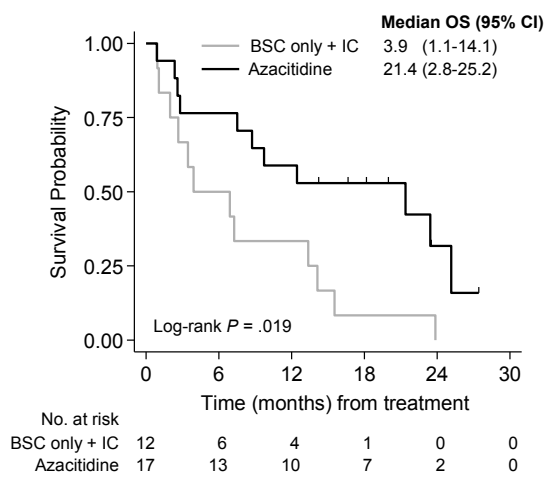
SUPPLEMENTARY FIGURES AND TABLES



Supplementary Figure S1. Patient flow of the study showing the selection process for patients in the current study. The diagram shows the number of patients with myelodysplastic syndromes (MDS) and myelodysplastic/myeloproliferative neoplasms (MDS/MPN) registered in the PHAROS MDS registry (*n* = 806). For the current study, we specifically selected 121 transplant-ineligible patients with intermediate-2 and high-risk MDS (collectively termed as higher-risk MDS, HR-MDS) on the International Prognostic Scoring System (IPSS). One patient with HR-MDS treated with lenalidomide was not included in the final group, as lenalidomide is a disease-modifying agent not routinely used for the treatment of HR-MDS. *Abbreviations*: SCT, stem cell transplantation; Int, intermediate; ESA, erythropoiesis-stimulating agent.



Supplementary Figure S2. A schematic overview of the study design.



Supplementary Figure S3. Overall survival among patients with intermediate-2 and high-risk myelodysplastic syndromes harboring -7/del(7q) abnormalities by treatment group. *Abbreviations*: BSC, best supportive care; IC, intensive chemotherapy.

Supplementary Table S1. Characteristics of patients with high-risk MDS by treatment group

	Treatment group						*P* value[a]	
	Azacitidine (n = 66)		BSC only (n = 37)		IC (n = 18)		Azacitidine vs BSC only	Azacitidine vs IC
	n	%	n	%	n	%		
Male sex	35	(53)	21	(57)	12	(67)	0.837	0.423
Age, years								
Median (range)	74 (55-84)		76 (52-88)		64.5 (46-75)		0.096	< 0.001
≥75	28	(42)	22	(59)	1	(6)		
Therapy-related MDS								
No	54	(82)	32	(86)	16	(89)	0.594	0.724
Yes	12	(18)	5	(14)	2	(11)		
Previous therapy for MDS								
No	47	(71)	34	(92)	14	(78)	0.022	0.768
Yes	19	(29)	3	(8)	4	(22)		
Hemoglobin, g/dL								
Median (range)	9.2 (6-12.9)		8.7 (4.5-14)		8.8 (5.5-11.6)		0.332	0.223
ANC, x 10^9/L								
Median (range)	1.1 (0.2-26.6)		1.35 (0.2-8.7)		1.0 (0.1-8.3)		0.701	0.942
Unknown	7	(11)	5	(14)	5	(28)		
Platelets, x 10^9/L								
Median (range)	42 (6-1128)		72 (5-467)		66.5 (10-250)		0.020	0.062
Bone marrow blasts, %								
Median (range)	12 (0-19)		12 (1-19)		14.5 (3-18)		0.870	0.071
IPSS cytogenetic risk								
Good	24	(36)	6	(16)	7	(39)	0.002	0.973
Intermediate	10	(15)	7	(19)	3	(17)		
Poor	29	(44)	13	(35)	7	(39)		
Not performed	3	(5)	11	(30)	1	(6)		
IPSS classification								
Intermediate-2 (int-2)	52	(79)	21	(57)	13	(72)	< 0.001	0.784
High	11	(17)	3	(8)	4	(22)		
At least int-2[b]	3	(5)	13	(35)	1	(6)		
Transfusion dependent[c]								
No	52	(79)	34	(92)	16	(89)	0.103	0.503
Yes	14	(21)	3	(8)	2	(11)		
Number of comorbidities								
Median (range)	1.5 (0-5)		2 (0-5)		1 (0-2)		0.678	0.007
Ferritin, µg/l								
Median (range)	621 (23-7164)		338.5 (85-3392)		1094 (49-2654)		0.053	0.429
Unknown	24	(36)	19	(51)	9	(50)		
LDH above ULN								
Median (range)	0.9 (0.6-3.7)		0.9 (0.5-3.7)		0.9 (0.5-5.7)		0.321	0.411
Unknown LDH	9	(14)	6	(16)	1	(6)		
Days since HR-MDS diagnosis								
Median (range)	33 (0-1630)		7 (-11 to 102)		39 (0-234)		< 0.001	1
HR-MDS at diagnosis	49	(74)	32	(86)	15	(83)	0.210	0.542
Treating hospital								
University	10	(15)	4	(11)	16	(89)	0.766	< 0.001
Non-university	56	(85)	33	(89)	2	(11)		
Azacitidine schedule	66	(100)	-	-	-	-	-	-
75 mg/m^2 per day for 7 days[d]	45	(68)	-	-	-	-	-	-
Other	11	(17)	-	-	-	-	-	-
Unknown	10	(15)	-	-	-	-	-	-

Abbreviations: BSC, best supportive care; IC, intensive chemotherapy; ANC, absolute neutrophil count; IPSS, International Prognostic Scoring System; IPSS-R, Revised IPSS; LDH, lactate dehydrogenase; ULN, upper level of normal; HR-MDS, higher-risk MDS. [a]Characteristics of patients were compared with the Fisher's exact test for categorical variables, and the Kruskal–Wallis test for continuous variables. *P*<0.05 indicated statistical significant differences. [b]Includes patients with at least intermediate-2 on the IPSS, but missing other parameters to complete calculate an IPSS score, mainly due to unperformed cytogenetics. [c]Transfusion dependency was defined as having at least one red blood cell transfusion every 8 weeks over a period of 4 months. [d]Including azacitidine for 7 consecutive days or a schedule of 7 days non-consecutive dosing with a 2-day break (that is, a 5-2-2 schedule).

Supplementary Table S2. Results of the Cox regression

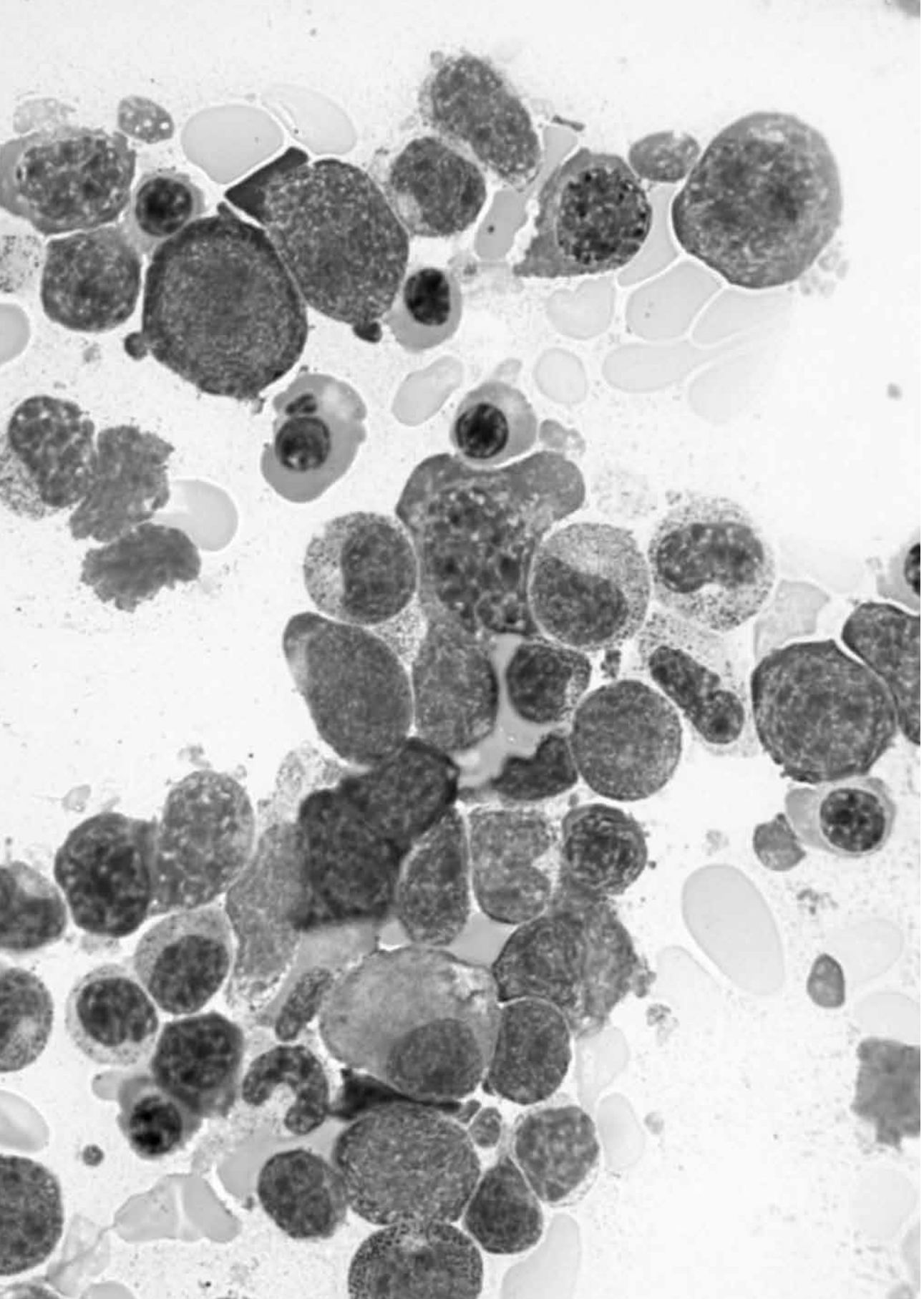
	BSC only vs azacitidine						IC vs azacitidine					
	Univariable			Multivariable			Univariable			Multivariable		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Treatment												
BSC only	1	-	-	1	-	-	-	-	-	-	-	-
IC	-	-	-	-	-	-	1	-	-	1	-	-
Azacitidine	0.65	0.41-1.02	0.063	0.61	0.38-0.97	**0.039**	0.89	0.49-1.59	0.687	0.88	0.48-1.64	0.699
Sex												
Male	1	-	-				1	-	-			
Female	1.42	0.92-2.20	0.122				1.42	0.84-2.39	0.189			
Age[a]	1.05	0.89-1.42	0.728				1.04	0.75-1.43	0.820			
IPSS cytogenetic risk												
Good	0.48	0.28-0.81	**0.007**	0.49	0.29-0.84	**0.009**	0.45	0.25-0.82	**0.010**	0.61	0.29-1.28	0.192
Intermediate	0.34	0.15-0.73	**0.006**	0.30	0.14-0.67	**0.003**	0.37	0.14-0.97	**0.042**	0.35	0.13-0.94	**0.037**
Poor	1	-	-	1	-	-	1	-	-	1	-	-
Not performed	1.02	0.54-1.93	0.950	0.91	0.47-1.74	0.769	0.73	0.25-2.12	0.562	0.89	0.27-2.92	0.852
Bone marrow blasts												
0-5%	1.38	0.68-2.77	0.370				1.93	0.83-4.46	0.126	1.78	0.65-4.86	0.261
5-10%	1.36	0.78-2.37	0.281				1.91	1.05-3.48	**0.034**	2.07	1.00-4.26	**0.049**
11-20%	1	-	-				1	-	-	1	-	-
Unknown	0.92	0.44-1.91	0.826				3.50	0.46-26.4	0.224	2.24	0.28-18.10	0.451
Hemoglobin <10 g/dL												
No	1	-	-	1	-	-	1	-	-	1	-	-
Yes	1.97	1.15-3.37	**0.013**	2.11	1.22-3.65	**0.008**	2.21	1.12-4.39	**0.023**	2.49	1.22-5.07	**0.012**
ANC <1.8 x 10^9/L												
No	1	-	-				1	-	-			
Yes	0.64	0.40-1.04	0.070				0.67	0.38-1.17	0.157			
Unknown	1.43	0.66-3.11	0.360				0.69	0.29-1.65	0.406			
Platelets <100 x 10^9/L												
No	1	-	-				1	-	-			
Yes	0.68	0.41-1.13	0.138				0.68	0.37-1.27	0.228			
Transfusion dependent[b]												
No	1	-	-				1	-	-			
Yes	1.07	0.81-1.44	0.606				1.17	0.86-1.59	0.318			
Therapy-related MDS												
No	1	-	-				1	-	-			
Yes	1.00	0.55-1.81	0.993				1.05	0.51-2.14	0.895			
Number of comorbidities[c]	0.94	0.80-1.11	0.486				0.92	0.77-1.10	0.353			
Days since HR-MDS diagnosis[d]	0.95	0.89-1.01	0.115				0.96	0.92-1.02	0.182			

Abbreviations: BSC, best supportive care only; IC, intensive chemotherapy; HR, hazard ratio; CI, confidence interval; IPSS, International Prognostic Scoring System; ANC, absolute neutrophil count. [a]Linear with estimates of HRs for 10-year age difference. [b]Transfusion dependency was defined as having at least one red blood cell transfusion every 8 weeks over a period of 4 months. [c]Linear with estimates of HRs for 1 comorbidity difference. [d]Linear with estimates of HRs for 1 month difference. Bold denotes statistical significance (that is, $P<0.05$). All variables with $P<0.05$ in univariate analysis were included in the multivariate analysis. Treatment group was included in the multivariate model regardless of the *P* value.

Supplementary Table S3. Number of azacitidine cycles received by patients according to response type

			Azacitidine cycles	
	n	**(%)**	**Median**	**Range**
Time to best response	32	(100)	5	1-12
Complete remission	8	(25)	6.5	4-9
Partial remission	2	(6)	5.5	5-6
Marrow CR	10	(31)	6.5	5-12
Hematological improvement only[a]	12	(38)	2.5	1-5
Azacitidine cycles after best response			8.5	0-25
Total no. of cycles by response type	66	(100)		
Any response[b]	32	(48)	13.5	3-26
Complete remission	8	(12)	13.5	5-25
Partial remission	2	(3)	5.5	5-6
Marrow CR	10	(15)	13	7-18
Hematological improvement only[a]	12	(18)	16	3-26
Stable disease[c]	8	(12)	6	2-18
Progressive disease[d]	20	(30)	4	1-20
Not evaluated[e]	18	(27)	7.5	1-26

Hematological response and improvement were assessed according to the International Working Group (IWG) 2006 criteria for MDS. *Abbreviations*: CR, complete remission. [a]Includes 5 patients who failed to achieve a hematological remission (that is, stable disease or progressive disease) and 7 patients who did not underwent a bone marrow assessment to evaluate hematological remission. Bone marrow assessments were always performed at the discretion of the treating physician. [b]Any response includes patients who achieved a complete remission, partial remission, marrow CR or hematological improvement with or without stable disease. [c]Includes 3 patients who achieved a hematological improvement. [d]Includes 2 patients who initial achieved a hematological improvement before showing signs of disease progression in the bone marrow. [e]Includes 7 patients who achieved a hematological improvement.



Summary and general discussion

8

1. SUMMARY

The main aim of this thesis was to progress our understanding on different epidemiologic aspects of myelodysplastic syndromes (MDS), chronic myelomonocytic leukemia (CMML) and acute myeloid leukemia (AML) at the population level in the Netherlands. These aspects include surveillance of the cancer burden, guideline adherence concerning diagnostics and therapy, and comparative effectiveness research. Population-based registries are useful instruments to study all patients within a well-defined area, so as to overcome patient selection which is always at hand in clinical intervention studies. The work described in this thesis utilized three Dutch population-based registries to unravel real-world characteristics and management of patients with MDS, CMML and AML, namely (i) the nationwide population-based Netherlands Cancer Registry (NCR), (ii) the Dutch medical claims-based DBC Information System and (iii) the Dutch **P**opulation-based **HA**ematological **R**egistry for **O**bservational **S**tudies in MDS and CMML—the PHAROS MDS registry.

In **chapters 2 to 4**, we assessed the clinical epidemiology of MDS, CMML and AML in the Netherlands using data from the NCR that covers the entire Dutch population. In **chapter 2**, we assessed trends in incidence, primary treatment and relative survival among patients diagnosed with MDS in the Netherlands between 2001 and 2010. The annual age-standardized incidence rate (ASR) of MDS initially increased but became stable as of 2007 at around 2.8 per 100,000 persons. The increase was presumably as a result of augmented disease awareness and improved case ascertainment to the NCR, rather than alterations in etiologic determinants. The age-specific incidence of MDS increased progressively after the age of 60, with the highest incidence among those above age 80 (32.1 per 100,000 persons in the period 2006-2010). The proportion of MDS cases without a diagnostic subtype decreased over time from 60% in 2001 to 36% in 2010. This finding may also be supported by the notion of augmented disease awareness over time, resulting in better classification. Of all patients, 89% received supportive care only. Treatment patterns did not change over time. Relative survival of patients with MDS decreased with older age and did not improve over time. Five-year relative survival was 59, 52, 41, 36 and 29% among patients aged 18-49, 50-59, 60-69, 70-79 and ≥80 years in the period 2001-2010, respectively. The lack of improvement may be explained by the conservative treatment approach over time and the scarcity of therapeutic options. In **chapter 3**, we assessed trends in incidence, primary treatment and relative survival among patients diagnosed with CMML in the Netherlands between 1989 and 2012. CMML is a very rare malignancy that predominantly affects older adults, with a median age at diagnosis of 76 years in the period 2007-2012. The annual ASR of CMML initially increased, but became stable as of 2008 at around 0.4 per 100,000 persons. The use of

chemotherapy decreased with older age. Hematopoietic stem cell transplantation (HSCT) was only applied in less than 5% of patients below age 70. Treatment patterns as well as relative survival did not change over the past decades. Five-year relative survival was poor in CMML irrespective of age, namely 21, 23, 20 and 12% for patients aged 18-59, 60-69, 70-79 and ≥80 years, respectively. The inferior and perpetual prognosis in CMML may be explained by the limited availability of CMML-specific interventions, as treatment approaches in CMML are often extrapolated from the knowledge gained in MDS. In **chapter 4**, we investigated patterns of treatment, trial participation and survival among patients with AML diagnosed between 1989 and 2012. The application of allogeneic HSCT (alloHSCT) increased over time among patients with AML up to age 70, whereas patients above age 70 predominantly received supportive care only. Around 60% of patients with AML up to age 60 participated in a clinical AML trial whenever open for accrual in the Netherlands. Despite that AML is a common disease of old age, with a median age at diagnosis of 68 years in the period 2007-2012, trial participation decreased progressively after the age of 60, with participation rates of 30 and 12% among patients age 61-70 and >70, respectively. Relative survival of patients with AML increased steadily in a span of more than two decades among patients up to age 70. Five-year relative survival in the period 2007-2012 was 54, 38, 14 and 2% for patients with AML age 18-40, 41-60, 61-70 and ≥70, respectively. Turning to patients with acute promyelocytic leukemia (APL), which is a distinct subtype of AML with specific biologic, molecular and clinical characteristics, as well as different management than AML, the use of chemotherapy increased over time across all age groups. Also, relative survival increased over time across all age groups and was most prominent among patients above age 60. Five-year relative survival in the period 2007-2012 was 84, 75, 54 and 37% for patients with APL age 18-40, 41-60, 61-70 and ≥70, respectively. Collectively, the steadily improved survival among patients with AML (up to age 70) and APL may be related to the increased use of intensive, potentially curative therapy over time. In addition, specific clinical trials should be designed for patients who are not eligible for current clinical AML trials in order to advance treatment strategies and improve outcomes, especially, but not exclusively, for patients above age 70.

It was recently demonstrated by the few available medical claims-based studies, which were conducted in the United States and Australia, that MDS and other myeloid neoplasms may be underreported in population-based cancer registries. As this phenomenon was not investigated in the Netherlands, we set out to investigate whether MDS and CMML are underreported in the NCR (**chapter 5**). To address this and complement the NCR, we used data from the Dutch medical claims-based **D**BC **I**nformation **S**ystem (DIS) to assess the incidence of MDS and CMML in the Netherlands between 2008 and 2010. Despite that the bone marrow examination is crucial to establish a diagnosis of MDS and CMML, we revealed that the diagnoses in the DIS were given without a bone marrow examination in almost half of all patients. Further, the performance of bone marrow examinations decreased sharply with older age. The ASR of MDS was almost twice as high when directly compared to recently updated estimates of the NCR, namely 5.4 vs. 3.3 per 100,000 persons. However, when we selected cases in the DIS based on bone marrow examinations alone, the incidence of MDS was similar to the NCR, namely 3.0 vs. 3.3 per 100,000 persons. Thus, the NCR might not have issues related to underreporting of MDS. As for CMML, the incidence was higher in the NCR compared to the DIS (0.2 vs. 0.4 per 100,000 persons), which we could not fully explain as the NCR includes cases that were confirmed by the physician through histology (bone marrow biopsy) and/or cytomorphology (bone marrow aspirate).

The studies described in chapters 2 and 3 provided valuable descriptive information on various epidemiologic aspects of MDS and CMML in the Netherlands based on data from the NCR. While this data is essential for Dutch cancer control activities, they are rather limited to address more specific questions regarding the delivery of care to patients with MDS and CMML. Therefore, in order to extend on particular findings described in chapters 2 and 3, the PHAROS MDS registry was established to document additional data complementary to the minimal dataset of the NCR. In **chapters 6 and 7**, the PHAROS MDS registry was utilized to provide insight into the delivery of care to patients with MDS and CMML in order to improve the quality of diagnosis and management of MDS and CMML in routine clinical practice in the Netherlands. In **chapter 6**, we assessed patterns of diagnostic procedures and disease management among patients with MDS and CMML. The aim of the study was to evaluate the degree of adherence to clinical practice guidelines for MDS and CMML in the west part of the Netherlands (6.3 million inhabitants). We specifically determined adherence to guidelines for bone marrow morphology and cytogenetic assessments, as well as treatment. A large proportion of patients with MDS and CMML did not undergo a diagnostic work-up as recommended by guidelines. The percentage of bone marrow dysplasia in erythroid, granulocytic and megakaryocytic cell lineages were reported in 33, 43 and 30% of evaluable bone marrow aspirates, respectively. In addition, the bone marrow blast percentage was not reported in 17% of evaluable bone marrow specimens. Cytogenetic assessments were not performed in 46 and 42% of patients with MDS and CMML, respectively. Cytogenetics are incorporated in the International Prognostic Scoring System (IPSS) to predict clinical outcome and plan risk-adapted therapy in MDS. As a result of incomplete diagnostic work-up, mainly due to lack of cytogenetic information, accurate prognostication as per IPSS was not possible in almost half of all patients with MDS, which, in turn, might lead to inappropriate risk-adapted management. Multivariable logistic regression analysis showed that older patients, patients with two or more comorbidities, patients diagnosed in non-university hospitals

and patients who did not receive prior cytotoxic therapy for an antecedent malignancy had lower odds to undergo cytogenetic assessments. Clinical practice guidelines in MDS generally recommend that patients with lower-risk disease by IPSS should mainly receive erythropoietic stimulating agents (ESAs) to correct anemia, whereas patients with higher-risk disease by IPSS should receive anti-neoplastic therapy (e.g. azacitidine, intensive chemotherapy or alloHSCT). However, against the recommendations set by clinical practice guidelines, a subset of patients with lower-risk MDS received azacitidine, while a subset of patients with higher-risk MDS received treatment with ESAs. Furthermore, patients with advanced age, poor performance status and an undetermined IPSS, as well as patients diagnosed in non-university hospitals had lower odds of receiving anti-neoplastic therapy. Similar analyses for CMML were precluded as a result of limited patient numbers within certain strata. Future studies will be needed to determine whether guidelines for the diagnosis and treatment of patients with MDS and CMML will be followed more stringently over time. In **chapter 7**, we set out to assess the effectiveness of azacitidine compared with best supportive care (BSC) only and intensive chemotherapy for the treatment of transplant-ineligible patients with exclusively higher-risk MDS in the Netherlands. Median overall survival was 14.6, 7.3 and 14.3 months for patients who received azacitidine, BSC only and intensive chemotherapy, respectively. Multivariable Cox regression analysis revealed that treatment with azacitidine was significantly associated with better survival relative to BSC only, whereas outcome with azacitidine relative to intensive chemotherapy was similar. However, patients treated with intensive chemotherapy spend significantly more days hospitalized than azacitidine-treated patients (median days, 71 vs. 2.5). Patients who achieved any response to azacitidine (48%) had superior overall survival than patients who did not responded (52%); they received a median of 13.5 and 5 cycles, respectively. In the overall series, azacitidine-treated patients received a median of 8.5 treatment cycles. The effectiveness of azacitidine in Dutch routine clinical practice was comparable with the results of the trial that led to its approval (i.e. the AZA-001 trial), in terms of prolonging overall survival and the overall administration of azacitidine cycles. However, patients in routine clinical practice fared much worse than patients in the AZA-001 trial, which may suggests that the trial population is not entirely representative of patients with higher-risk MDS from the general population.

2. GENERAL DISCUSSION

This final part of the thesis will discuss the main findings of the thesis in the context of current knowledge and their possible implications to change clinical as well as cancer registration practice, followed by future perspectives for continuing population-based cancer registry research on hematological malignancies at the national and international level.

2.1 Cancer surveillance

The first population-based cancer registries were founded 70 years ago.[1] Since then, their main purpose remained, which is to provide statistics on the incidence of cancer according to time, geographic region, as well as demographic, clinical and tumor characteristics. Cancer registration in the Netherlands was initiated in the 1950s at the regional level and became nationwide since 1989. Since its establishment in 1989, the nationwide population-based Netherlands Cancer Registry (NCR) is still the authoritative source for cancer surveillance in the Netherlands. What makes the NCR unique from most other cancer registries is that is also records information on primary treatment across the entire registry. In this paragraph, we will discuss the outcomes of the studies performed with data from the NCR to delineate the clinical epidemiology of myelodysplastic syndromes (MDS), chronic myelomonocytic leukemia (CMML) and acute myeloid leukemia (AML) in the Netherlands. We will end this paragraph by discussing the possible concerns related to the underreporting of MDS and CMML in the NCR.

2.1.1 Incidence of MDS

The initial increase in MDS incidence was likely a reflection of augmented disease awareness since the introduction of the World Health Organization (WHO) 2001 classification of MDS,[2] which has resulted in an increased diagnosis of MDS, particularly among older adults (**chapter 2**). Interestingly, an increase in MDS incidence has also been documented in population-based studies conducted in the United States,[3,4] Germany (Düsseldorf),[5,6] France (CÔte d' Or)[7] and Spain (Girona).[8] So far, the incidence only leveled off in Germany (Düsseldorf).[6] In addition, the incidence rates in our study were similar to those reported in the abovementioned studies as well as those reported in the United Kingdom.[9]

Augmented awareness of MDS in the Netherlands also contributed that the proportion of MDS cases with a diagnostic subtype increased over time, especially refractory cytopenia with multilineage dysplasia (RCMD) which is a diagnostic subtype that has been introduced since 2001 (**chapter 2**). The increase probably reflects that physicians, cytomorphologist and pathologist became increasingly familiar with the diagnostic classification of MDS according the WHO criteria. Still, 36% of all MDS cases

were not otherwise specified (MDS NOS) in 2010, which suggest that the classification of MDS in routine clinical practice seems challenging. A relatively high proportion of MDS NOS cases was also observed in population-based cancer registry studies conducted in the United States (56%)[4] and Spain (28%).[8] By contrast, all MDS cases recorded in the Düsseldorf MDS registry are classified into a diagnostic subtype.[10] The Düsseldorf MDS registry is a specialized MDS registry that includes all patients that are diagnosed with MDS in the Greater Düsseldorf area since 1982.[10] The most likely explanation for the absence of MDS NOS cases in that registry is that all bone marrow aspirates of patients with (suspected) MDS are reviewed centrally by experienced hematologists of the Heinrich Heine University in Düsseldorf, Germany. At present, for routine diagnostic purposes, the bone marrow morphology assessment in the Netherlands is generally not performed centrally within a center with specific hematologic competence (i.e. teaching or university hospital). Instead, it is often performed in hospitals where patients were initially diagnosed, which are mainly general hospitals. So, in order to improve the diagnostic classification of MDS in routine practice, health care professionals should more cautiously follow the recommendations of the current WHO (2008) classification of MDS. To this end, in order to facilitate a standardized diagnosis of MDS, the MDS working party of the Dutch Hemato-Oncology Foundation for Adults in The Netherlands (HOVON) published a guideline for the diagnosis of MDS in 2013,[11] which largely follows the recent recommendations set by the European Leukemia Network (ELN) for the diagnosis of MDS.[12] In addition, centers that are less experienced in bone marrow morphology assessment should send bone marrow specimens to a center with specific hematological competence to allow for an accurate classification of MDS, preferably to a center that offers an integrated diagnostic approach including all facets of MDS diagnosis (i.e. cytomorphology, histopathology, cytogenetics, molecular genetics and immunophenotyping).

2.1.2 Incidence of CMML

The antecedent rise in CMML incidence can most likely be explained by augmented CMML awareness over time, which resulted in an increased diagnosis of CMML, especially after the introduction of the WHO classification in 2001 (**chapter 3**).[2] In that classification scheme, CMML was recognized as a distinct disease entity rather than a specific subtype of MDS. Thus, physicians may became more familiar with the diagnostic criteria of CMML, as the WHO classification provides a detailed account on specific hematological and morphological characteristics of CMML. Interestingly, other population-based studies from the United States,[4] United Kingdom,[9] Germany (Düsseldorf),[10] France (CÔte d' Or)[7] and Spain (Girona)[8] report a similar ASR of CMML. In addition, a gradual increase in CMML incidence was also reported in studies conducted in France (CÔte d' Or)[7] and Spain (Girona).[8]

2.1.3 Incidence of AML

The overall ASR of AML in the Netherlands, which remained relatively stable during the entire study period of 1989-2012 **(chapter 4)**, was similar to those in the United Kingdom[9] and Spain,[8] but slightly higher in the United States,[13] Sweden[14] and Denmark.[15] Several reasons can be put forward to explain the somewhat lower incidence rates in the Netherlands. The ASR of AML in Sweden and Denmark is higher because the cancer registries in those countries include, next to primary and therapy-related AML, AML arising after MDS, CMML or a myeloproliferative neoplasm (MPN), that is, secondary AML.[14,15] In the NCR, secondary AML was not standardly and consistently recorded across the entire registry. To allow standardized registration of secondary AML in the NCR, recommendations set by the European Network of Cancer Registries (ENCR) on the registration of progressions, transformations and multiple diagnoses of hematological malignancies are implemented by the NCR for cases diagnosed as from January 1, 2014.[16] So, in the near future, the NCR can also provide valuable clinical and epidemiological information on secondary AML at the population level.

2.1.4 Incidence of APL

Epidemiological studies on APL are rather scarce, primarily as a result of the rarity of this distinct subtype of AML to study meaningful epidemiological trends, which requires a large geographic region, sufficient patient numbers, as well as long-term study and follow-up period. Fortunately, the NCR allows for studying meaningful epidemiologic trends in APL. As shown in this thesis in **chapter 4**, the incidence rate and the median age at diagnosis of APL in the Netherlands were similar to those reported in a population-based study conducted in Sweden.[17] In addition, it seems that APL is less often diagnosed in northwest European countries as compared to south European countries[18] as well as the United States.[19,20] The differences may be explained by genetic and/or environmental factors, especially among Latinos. This hypothesis is as yet not tested at the entire European level.

2.1.5 Treatment and survival of MDS and CMML

For both MDS (**chapter 2**) and CMML (**chapter 3**), primary treatment and relative survival remained essentially unchanged over the entire study period in the Netherlands. In the overall series, we showed that primary treatment in MDS and CMML mainly consisted of supportive care only. Even among younger patients who are generally candidates for intensive, potentially curative therapy, provided that they have high-risk disease features, the application of chemotherapy and/or HSCT was comparatively low and did not increased over time. In general, treatment options in MDS and CMML are limited, especially for older patients who are largely not eligible for curative treatment

approaches such as intensive chemotherapy and alloHSCT. Altogether, this may in turn resulted in that relative survival of MDS and CMML did not improve over time across all age groups. A limitation of the NCR is that it only records primary treatment. Patients with MDS and CMML do not necessarily require specific treatment immediately after diagnosis, because a subset of patients may have relatively mild cytopenias at presentation, which can remain stable for many years with few symptoms, as well as exhibit a relatively low chance to progress to AML. This might explain, in part, the high proportion of patients who receive supportive care only as primary treatment. Patients who later in their disease course experience worsening of cytopenias or progress to AML may require specific therapy. However, information on subsequent therapy is not yet recorded in the NCR.

Another limitation of the NCR is that it lacks information across the entire registry on the specific type of treatment. More specifically, the definition of chemotherapy in the NCR is a broad category that includes intensive chemotherapy, hypomethylating agents (e.g. azacitidine) and hydroxyurea. In addition, the NCR also lacks information across the entire registry on important prognostic factors, such as comorbidities and the International Prognostic Scoring System (IPSS) risk for MDS.[21] Thus, the NCR is currently limited to assess whether treatment decision-making largely followed clinical practice guidelines concerning diagnosis and management.[12,22-24]

2.1.6 Treatment, trial participation and survival of AML

The population-based study on treatment, trial participation and survival of AML that is described in **chapter 4** is a decent example that data from population-based cancer registries can be enriched with data from other registries/databases. For that particular study, we enriched the NCR with information on the type of HSCT—that is, allogeneic or autologous HSCT (autoHSCT)—and clinical trial participation, as both type of parameters are not recorded in the NCR.

Treatment and survival of patients with AML aged 18 to 70 years

In **chapter 4**, we showed that relative survival of patients with AML age 70 or younger increased steadily over time since the early 1990s. The improvement was most notable among patients aged 18 to 60 years, especially in the most recent study period (2007-2012), whereas improvement among patients aged 61 to 70 years considerably lagged behind and was comparatively poorer. The most likely explanation for the improvements in relative survival might be related to better post-remission approaches such as consolidation chemotherapy, autoHSCT and alloHSCT, as well as better supportive care and improved risk-adapted therapy. More specific analyses among patients aged 18 to 60 years, in which the major improvement had taken place, revealed that those treated with chemotherapy and/or autoHSCT, as well as those who received alloHSCT showed improved outcome over time. Our findings are congruent with those reported in Sweden, which also showed improved outcome over time,[14] especially in regions where intensive therapy is more often applied.[25-27]

The question for future clinical studies is whether current risk stratification models can be refined to more accurately identify specific patient subsets who would likely benefit from a particular post-remission strategy. Subsequently, population-based studies are needed to confirm whether improved risk-adapted therapy would translate into improved outcome among patients in routine practice. Concerning the population-based study in AML that is described in **chapter 4**, the NCR did not have information on cytogenetics, molecular genetics and other important prognostic factors to determine the leukemia risk profile. Thus, we were unable to actually demonstrate whether patients with a favorable risk AML increasingly received consolidation chemotherapy and patients with an intermediate or adverse risk AML increasingly underwent alloHSCT. One thing is, however, sure: the outcome of patients with AML up to age 70 is increasing steadily over time in the Netherlands since the early 1990s.

Treatment and survival of patients with AML older than 70 years

The work described in **chapter 4** showed no notable trends in treatment and relative survival among patients with AML above age 70. The vast majority of these patient received supportive care only throughout the entire study period. Also, perhaps as a result of this conservative treatment approach over time, relative survival among these patients remained unchanged and comparatively poor with a 5-year relative survival rate of 2% in the most recent study period (2007-2012). In a landmark trial that was published by Löwenberg *et al*. in 1989, intensive remission induction chemotherapy prolonged survival compared with supportive care only among patients with AML aged 65 years or older.[28] In addition, population-based data from the Swedish Acute Leukemia Registry, which were published by Juliusson *et al.* in 2011, suggested that most patients with AML aged 70 to 79 years may tolerate and benefit from intensive chemotherapy compared with palliation alone.[29,30] In that study, 55% of all patients aged 70 to 79 years received intensive chemotherapy.[29] By contrast, based on information from two regional cancer registries in the Netherlands, around 20% of patients with AML above age 70 received intensive chemotherapy (**chapter 4**). The reason for the comparatively low administration of chemotherapy among elderly patients in the Netherlands is unknown at this time, but might be due to the physician's attitude towards administering intensive chemotherapy to elderly patients. In other studies based on data from the Swedish Acute Leukemia Registry, regional practice variation was found in the provision of intensive chemotherapy to patients with AML aged 70 to 79 years.[25,26] Better outcome among this particular age group was predominantly observed in health care regions where more patients were given intensive chemotherapy. As a result of this practice variation, national guidelines

for the treatment of AML were introduced in Sweden to reduce that variation. Altogether, eligibility for intensive therapy should not be solely an age-based decision.

For patients who are judged ineligible for intensive therapy, due to poor performance status and/or severe comorbidities, the hypomethylating agents azacitidine or decitabine may be alternative treatment approaches.[31] These two hypomethylating agents provide no curative solution, but may prolong overall survival in selected patients. Since 2009, azacitidine is approved by the European Medicines Agency for the treatment of transplant-ineligible patients with low-blast count AML (i.e. 20 to 30% blasts).[32,33] A recent phase 3 clinical trial, which was published by Dombret *et al.* in 2015, suggested that azacitidine may also be an alternative treatment approach for newly diagnosed patients with AML aged 65 years or older with more than 30% bone marrow blast.[34] However, as yet, azacitidine is not approved for that particular blast threshold. Although decitabine is registered as from 2012 for the treatment of patients with AML aged 65 years or older —according to the WHO classification (i.e. ≥20% blasts)—who are ineligible for intensive therapy, it can only be administered within university hospitals in the Netherlands. The debate is currently ongoing whether such treatment should be readily available in basically any hospital or that the provision of such therapy to older patients should be concentrated in centers with specific hematologic competence. Collectively, there is an unmet clinical need to augment the efforts to improve outcome among older, often unfit patients with AML. Therefore, under the auspices of HOVON, a clinical trial is currently planned for this specific older population, namely the phase 2 HOVON 135 trial. That trial is designed to assess the tolerability and efficacy of a 10-day decitabine schedule compared with new drugs, such as ibrutinib.

Trial participation of patients with AML

Although we showed in **chapter 4** that the majority of patients with AML aged 18 to 60 years were entered into a clinical trial, still around 40% did not. These relatively young patients could potentially be enrolled in a clinical AML trial, because there were consecutive clinical AML trials open for accrual in the Netherlands throughout the entire study period for that particular age group. Interestingly, around 90% of those patients who did not enter into a clinical trial still received intensive therapy (i.e. chemotherapy, autoHSCT or alloHSCT) outside the setting of a clinical trial. Furthermore, one would expect a representative sample of elderly patients with AML in clinical trials, seeing that AML is a disease of older adults. On the contrary, the accrual rates decreased disproportionally after the age of 60, with trial participation rates of 30 and 12% among those aged 61 to 70 years and above age 70, respectively (**chapter 4**). This result is in sharp contrast to those recently observed in a population-based study conducted among older patients with acute lymphoblastic leukemia (ALL) in the Netherlands.[35] In that study, 58% of patients with ALL aged 60 to 69 years entered in clinical ALL trials.[35] We cannot explain why there

is such a difference in trial participation between elderly patients with AML and ALL, as both acute leukemias are rapidly fatal if intensive therapy is not promptly initiated after diagnosis. Perhaps there is a degree of therapeutic nihilism for elderly patients with AML, whereas this seems less uncommon in ALL. It is obvious that continued underrepresentation of elderly patients with AML in clinical trials will not advance establishing an optimal treatment strategy for this particular age group. Besides, elderly patients who are currently enrolled in clinical trials might not be entirely representative for the general older AML population. Therefore, findings from clinical trials should be interpreted with caution, as such findings are unlikely to reflect the actual outcome of the total disease population.

A drawback of the study described in **chapter 4** is that the NCR does not record additional, more detailed information on patient- and disease-related characteristics that could potentially explain the possible reasons for non-inclusion. The following are potential issues that might be related to non-inclusion. First, patients might not be eligible due to stringent inclusion criteria. In the few available population-based studies,[36-38] which were regional in extent, the following characteristics were associated with non-inclusion: advanced age, secondary AML, prior malignancy, poor performance status and concomitant comorbidities.[36-38] Future studies will be needed to identify specific patient- and physician-related characteristics that could explain the reasons for non-inclusion. Together, this information may be crucial to design clinical trials with less stringent exclusion criteria or specifically tailored for particular subgroups that are currently excluded or underrepresented in clinical AML trials. Second, physicians might be reluctant to refer patients for clinical trial participation, possibly due to costs related to additional diagnostic and response assessments that cannot be (entirely) reimbursed, as it is not part of standard of care but nevertheless are required for the trial. Also, the complexity of the trial design might influence the physicians' attitude concerning patient enrollment. Third, the increasing bureaucracy of clinical trial regulations might delay the execution of clinical trials in hospitals, resulting in that patients cannot be directly offered the latest therapeutic possibilities. Lastly, patients might refuse to participate in clinical trials. Patients should, however, be encouraged to participate in clinical trials; the act of the physician is crucial for this. The physician should carefully explain to patients what the benefit-to-risk ratio is of trial participation, and that in such manner, that it is understandable to patients. Subsequently, patients should, in turn, make a decision based on accurate, yet understandable, information provided by physician. In general, participating in well-designed clinical trials may furnish advantages for patients. First, patients are offered the newest therapeutic possibilities that, in turn, may advance progress towards better treatment and consequently improved outcome. Secondly, the provision of care for patients in clinical trials may provide some guarantee for the quality of that care, as clinical trial protocols dictate how patients should specifically be treated and monitored during the trial.

2.1.7 Treatment and survival of APL

Before the introduction of all-trans retinoic acid (ATRA) for the treatment of APL, it was a highly fatal subtype of AML.[39] Since the implementation of ATRA with concurrent anthracycline-based chemotherapy in the early 1990s, APL became a highly curable disease.[39] Therefore, baseline relative survival in the earliest study period (1989-1994) was comparatively high among patients up to age 60 **(chapter 4)**. What is very encouraging is that the most notable survival improvement was observed among patients above age 60, which coincided with the increased application of chemotherapy over time in that age group. This is in stark contrast when compared with the provision of chemotherapy to patients with AML of the same age group (**chapter 4**). Perhaps physicians have a perception that intensive chemotherapy is more beneficial for older patients with APL than AML; although this is not entirely true, because older patients with AML may also tolerate and benefit from intensive therapy.[26,28-30] While information on the use of ATRA was by that time not recorded in the NCR, it is indisputable that contemporary treatment with ATRA and concurrent anthracycline-based chemotherapy as standard of care for patients with APL contributed to the remarkable improvement among the elderly. More recently, arsenic trioxide (ATO) with ATRA has been shown to produce similar, if not better, outcome compared with ATRA with chemotherapy.[40,41] ATO is less toxic than chemotherapy-based regimens; however, it is as yet not registered in the Netherlands for routine use in APL.

Despite that relative survival in APL improved over time, early death rates—that is, death within 30 days after diagnosis—remained comparatively high and unchanged over the past two decades (**chapter 4**), a phenomenon also observed in other population-based studies in APL.[17,20] Early death rates may potentially be reduced if clinical features, and especially morphologic and genetic features, are timely recognized, patients are immediately transferred to a specialized hospital, and specific treatment and supportive measures to counteract the coagulopathy are promptly initiated after a (suspected) diagnosis of APL.[42]

Generally, overall outcomes of patients with APL at the population level are inferior than those reported in recent clinical series.[43-47] This is congruent with other population-based series from the United States and Sweden.[17,20] The assessment of trial participation among patients with APL was outside the scope of this thesis. However, patients with APL at the population level were older than those enrolled in clinical APL trials.[40,44,48,49] This may suggest that older patients with APL fail to enter in clinical studies, presumably due to higher early death rates and poor performance status. Moreover, in an unselected Swedish APL population, early death increased stronger with poorer performance status than with older age.[17] Altogether, the discrepancy in populations between those recruited and those not recruited in clinical trials might explain the differences in outcome.

2.1.8 Underreporting of MDS

Recent studies using medical claims-based methodologies, which were conducted in the United States and Australia, raised concerns about the possible underreporting of MDS in population-based cancer registries.[50,51] In the study described in **chapter 5**, we employed a similar medical claims-based methodology by using data from the nation-wide Dutch medical claims-based **D**BC **I**nformation **S**ystem (DIS) to assess whether MDS could be underreported in the NCR. We showed that the incidence of MDS was almost two times higher when directly compared to recently updated estimates of the NCR.[52] What is remarkable is that, upon further analysis of the total DIS cohort, we revealed that the diagnosis of MDS was given to 46% of patients without performing a bone marrow examination. A diagnosis of MDS can essentially not be established without a bone marrow confirmation and thus may be misdiagnosed and improperly managed.[12] Although not desirable, there might be several reasons why a bone marrow examination is not performed. First of all, a subset of patients might not consent to undergo a bone marrow examination, as they may perceive this procedure as very invasive. Secondly, a wrong tendency might exist to skip a bone marrow examination if the peripheral blood examination shows features suggestive of MDS such as cytopenias and dysplastic characteristics in one or more cell lineages. These characteristics, however, are not exclusive for MDS as other (malignant) disorders as well as effects of medications can mimic these features.[53] Lastly, a reluctance to complete a comprehensive diagnostic work-up, especially in elderly patients, might exist among physicians as they may perceive that therapeutic options in these patients are limited, and thus a comprehensive diagnostic work-up would not be informative for treatment decision-making. Whatever the reason may be to skip a bone marrow examination, clinical practice guidelines clearly state that the diagnosis of MDS should always be established through bone marrow examination.[11,12,23,24] In addition, information gained from such examination (e.g. percentage of blast) may aid in risk-adapted treatment decision-making.[11,12,23,24]

When we specifically calculated the incidence of MDS in the DIS cohort among patients who underwent bone marrow examinations, it was similar to the NCR. In contrast to the findings from the medical claims-based studies conducted in the United States and Australia,[50,51] we suggest that the incidence of MDS in the Netherlands seems unlikely to be underreported in the NCR. Nevertheless, it seems rather implausible that all cases without bone marrow examinations in the DIS were truly MDS. A proportion of these cases might be true MDS whenever the bone marrow was examined. The remaining cases might represent other disorders with MDS-like characteristics.

Collectively, our study implies the hypothesis that there is some evidence that the incidence of MDS might be underreported in the NCR. Unfortunately, diagnoses from the DIS could not be confirmed through retrospective medical records review, because of the

anonymous nature of the data. Therefore, we cannot confirm nor reject our hypothesis. In this regard, medical claims-based studies may complement the NCR to estimate the possible magnitude of underreporting. However, such results should always be interpreted with caution, as cancer registries remain the gold standard of any rational program in cancer surveillance. In addition, MDS might be underdiagnosed in the Netherlands as almost half of all diagnoses in the DIS were given without a bone marrow examination. We eagerly await future studies with data from the NCR to assess whether we may witness a secondary increase in incidence rates of MDS due to better awareness that the diagnosis should always be confirmed by bone marrow as stated in clinical practice guidelines for the diagnosis of MDS.[11,12,23,24]

2.1.9 Underreporting of CMML

At present, no study has assessed the possible underreporting of CMML in cancer registries. In **chapter 5**, we employed the same medical claims-based methodology using data from the nationwide DIS, which was discussed in the previous section for MDS, to assess whether CMML could be underreported in the NCR. Like in MDS, the diagnosis of CMML was given to almost half of all patients without performing a bone marrow examination. CMML can also essentially not be diagnosed without such examination.[54] What was rather surprising was that the incidence of CMML was somewhat higher in the NCR than in the DIS cohort among patients who underwent bone marrow examination. It is unlikely that the NCR includes cases that are not confirmed through histology and/or cytomorphology. Findings from this study implies that results from cancer registry studies and medical claims-based studies should always be placed next to each other for the correct interpretation of such results.

2.2 Guideline adherence in MDS and CMML

The next part of the discussion focuses on guideline adherence concerning diagnostics and treatment in MDS and CMML. The aim of contemporary clinical practices guidelines is to provide evidence-based recommendations for the standard of care to patients in specific areas of medicine in order to promote best clinical practice and limit practice variation in health care.[55,56] Clinical practice guidelines can essentially be regarded as guidance to both physicians and patients to select the most appropriate health care intervention that is based on the most up-to-date evidence and tailored to specific clinical situations.

2.2.1 Bone marrow assessment

We showed in **chapter 5**, based on information gained from Dutch medical claims, that a large proportion of patients with MDS and CMML were given the diagnosis

without a bone marrow examination. MDS and CMML may be misdiagnosed without a bone marrow examination. The NCR exclusively includes MDS and CMML cases that were confirmed by the physician through histology and/or cytomorphology (**chapters 2 and 3**). Therefore, information on MDS and CMML based on data from the NCR are largely representative for the general MDS and CMML population. However, information recorded in the NCR is insufficient to assess more in-depth aspects of guideline adherence such as assessment of bone marrow dysplasia, prognostication by means of cytogenetic assessment, and risk-adapted treatment decision-making. The PHAROS MDS registry was established for that particular reason; to assess in more detail whether recommendations set by clinical practice guidelines for the diagnosis and management of MDS and CMML were adhered to.

In **chapter 2,** we showed with NCR data that more MDS cases were classified into a diagnostic subtype over time. However, as described in **chapter 6**, we showed with data from the PHAROS MDS registry that the morphologic assessment of dysplasia leaves much to be desired, as the degree of dysplasia in erythroid (excluding ring sideroblasts), granulocytic and megakaryocytic lineages were reported in 33, 43 and 30% of evaluable bone marrow aspirates, respectively. In the majority of cases, the cytomorphology reports describe the type of dysplasia without the degree of dysplasia. However, information on both the type and degree of dysplasia is necessary to distinguish between various subtypes, which is especially relevant for MDS subtypes with bone marrow blasts below 5% (i.e. refractory cytopenia with unilineage vs. multilineage dysplasia).[2,57] While virtually all bone marrow aspirates where evaluable in our study (96%), the reluctance to report the degree of dysplasia is most likely not related to the poor quality of bone marrow slide preparations. Therefore, more emphasis should be placed to more cautiously assess the degree of morphologic bone marrow dysplasia to facilitate a more accurate classification of MDS. In situations where the morphology assessment of bone marrow dysplasia is challenging—for example, due to poor quality of bone marrow slide preparations or interobserver discordance—flow cytometry immunophenotyping, according to the methodology set by the International Flow Cytometry Working Group within the ELN,[58-60] can objectively measure the type and degree of dysplasia in both mature and immature compartments of different bone marrow cell lineages.[12,61,62] More specifically, flow cytometry immunophenotyping can identify particular aberrancies that are otherwise not detected through bone marrow morphology assessment. Despite the importance of morphologic and immunophenotypic dysplasia assessment in MDS and CMML, no single sign of dysplasia is typical for these disorders.[63] For that reason, other causes of dysplasia should always be ruled out.[53] Of note, flow cytometry immunophenotyping can also be utilized to enhance prognostication by adding particular flow cytometric parameters to the IPSS[64] and its revision (IPSS-R).[65] More importantly,

flow cytometry-based scoring systems, which are as yet not standardly included in the IPSS and IPSS-R, can identify specific patient subsets within the lower-risk categories of the IPSS and IPSS-R with poor prognosis. The WHO classification systems as well as clinical practice guidelines recommend that 500 nucleated bone marrow cells should be enumerated in the bone marrow smear.[11,12,23,24,54,57] In **chapter 6**, we showed that the percentage of bone marrow blasts were not reported in 17% of evaluable bone marrow specimens. We hypothesize that cases in which the blast percentage was not reported could potentially be those with blasts below 5% in the bone marrow, as blasts above 5% in the bone marrow may be less challenging to count (or recognize) than lower blast percentages. The bone marrow blast percentage is, however, not only important for the classification of MDS and CMML, but also, perhaps even more important, for prognostic purposes. Generally, the higher the blast count, the poorer the outcome. Therefore, the bone marrow blast percentage is integrated in specific prognostic scoring systems for MDS and CMML, along with other prognostic parameters such as the karyotype.[21,66,67]

2.2.2 Cytogenetic assessment

The karyotype is a major component of the IPSS, which is regarded as the reference standard for predicting prognosis and planning risk-adapted therapy in MDS.[11,12,21-24] Of note, there is currently no European consensus for CMML concerning a reference standard for prognostication and treatment decision-making.[68] In addition, cytogenetic testing is required for the classification of MDS, namely for MDS with isolated del(5q).[57] Also, cytogenetic testing in the setting of CMML is required to exclude particular MPNs, such as chronic myeloid leukemia [t(9;22)] and MDS/MPN with eosinophilia [t(5;12)].[54] Therefore, cytogenetic assessment is a mandatory diagnostic procedure in MDS and CMML.[11,12,23,24,54] However, as shown in **chapter 6**, a substantial proportion of patients with MDS and CMML did not undergo cytogenetic assessments (46 and 42%, respectively). Consequently, as a direct result of unperformed cytogenetics, an IPSS risk group could not be determined in these patients, which, in turn, may lead to inaccurate prognostication, possibly resulting in uninformed treatment decision-making. Our results are in agreement with other population-based studies conducted in Germany and Poland.[69,70] It is unlikely that cost-related issues would be prohibitive to perform cytogenetic analysis in the Netherlands, as all residents in the Netherlands are obliged by law to take out a health care insurance policy (**chapter 5**). The possible reasons for not performing cytogenetic assessments were discussed in **chapter 6**. By multivariable logistic regression analysis, patients who received previous cytotoxic therapy were more likely to undergo cytogenetic assessments, as physicians might be more aware that those patients could potentially have a therapy-related malignancy and hence implications for treatment decision-making. In addition, patients who were diagnosed in university hospitals were more likely to undergo cytogenetic assessments (**chapter 6**). This could be explained by the fact that physicians from university hospitals more strictly adhere to clinical practice guidelines. In addition, patients may be referred to university hospitals for a comprehensive diagnostic work-up, as it may be anticipated that particular patients might be eligible for intensive therapy, which is generally provided in university hospitals. Nevertheless, advanced age and an increasing number of comorbid conditions were both independently associated with not performing cytogenetic assessments. While most older, often comorbid patients might not be candidates for a specific treatment approach, risk stratification by IPSS is essential to counsel patients about their life expectancy. Therefore, a comprehensive diagnostic approach, including cytogenetic assessment, should not depend on the *a priori* perception that a patient is not eligible for treatment.

Despite we showed in **chapter 6** that the IPSS and IPSS-R could segregate patients into several risk groups with distinct outcome, the median survival rates were lower than those reported in the index papers. This all goes to say that patients included in the establishment of prognostic models may not entirely be representative of the general patient population. Nevertheless, the IPSS-R could more effectively segregate patients than the initial IPSS and was in accordance with the IPSS-R index paper, as well as several other independent validation studies.[66,71,72] Therefore, the prognostic utility of scoring systems should always be validated among the general patient population.

2.2.3 Treatment of MDS

We showed in **chapter 6** that treatment recommendations were not always followed, because some patients with lower-risk MDS received azacitidine, whereas some patients with higher-risk MDS received ESAs. In the Netherlands, azacitidine is only registered for use in patients with higher-risk MDS who are not eligible for alloHSCT. There might be clinical circumstances to provide these patients with alternative treatment options, for example in the case of failure after conventional strategies for lower-risk MDS. Nevertheless, whatever the circumstance may be, azacitidine is not indicated for that particular risk group and extreme caution should be taken when azacitidine is used outside the registered indication. As for the administration of ESAs in patients with higher-risk MDS, physicians might still not be fully aware that patients within that particular risk group have a very low probability of response to ESAs.[73,74] We also showed that patients with an undeterminable IPSS mainly received supportive care modalities (**chapter 6**). Although speculative, physicians might *a priori* decide that certain patients (those with an undetermined IPSS) would not benefit from a specific therapy and thus a comprehensive diagnostic approach would not change their treatment plan. However, it can be argued that a well-informed treatment plan can essentially not be made without accurate

prognostication, as this manner of treatment decision-making is not according to the guidelines and thus can be considered as diminished quality of care. Therefore, guidelines for the diagnosis and risk-adapted treatment in MDS should be followed more stringently.

The results described in **chapter 6** also revealed findings that confirmed certain gut feelings. For instance, advanced age and poor performance status were independently associated with the reticent use of anti-neoplastic therapy. The physician may decide to refrain from such therapy, as anti-neoplastic therapy in this patient population might lead to more harms than benefits. In this regard, deviating from clinical practice guidelines may be considered as good quality of care, as it is essential to prevent treatment-related mortality or morbidity. However, low-intensity, disease-modifying agents such as azacitidine and lenalidomide may be particularly suitable for patients who are not able to undergo intensive therapy due to advanced age, poor performance status or concomitant comorbidities. Interestingly, and somewhat unexpected, the presence of two or more comorbidities compared with no or one comorbidity did not influence the decision to provide anti-neoplastic therapy. Therefore, therapy selection should not solely be based on age and poor performance status. For example, poor performance status does not necessarily have to be related to concomitant comorbidities; rather, it can be related to the MDS (e.g. due to cytopenia). The initiation of specific therapy may modify the disease course of MDS and consequently may ameliorate the initial poor performance status. In fact, although not shown in MDS, data from the Swedish Acute Leukemia Registry showed that the provision of intensive chemotherapy to patients with AML who have poor performance status resulted in lower early death rates than those who received palliation alone, irrespective of age.[26] Thus, providing supportive care only will certainly not tackle the problems in patients with symptomatic MDS. Although we did not assessed the effect of a specific comorbidity on MDS treatment decision-making, it is well known that specific comorbidities, such as cardiac and renal, can affect prognosis in MDS independent of well-established prognostic factors in MDS.[72,75,76]

Participation of patients with MDS in clinical trials should be encouraged, as only 5% entered in clinical trials. On the other hand, the low participation rate, which is in contrast with the comparatively overall higher rate of trial participation among older patients with AML (**chapter 4**) and ALL,[35] could be explained by the notion that patients may not be eligible for current clinical trials in MDS.

2.2.4 Treatment of CMML

At present, clinical practice guidelines for CMML are controversial and ill-defined. This is mainly as a result of the scarcity of specific phase 3 clinical trials in CMML which are essential to establish evidence-based clinical practice guidelines. Indeed, we showed in

chapter 6 that only 1% of patients with CMML entered on a clinical trial. Most treatment recommendations in CMML, expect the use of hydroxyurea,[77] are usually extrapolated from the knowledge and experience gained in MDS.[32,78] The results described in **chapter 6** showed that most patients with CMML received typically MDS-like therapy such as red blood cell transfusions, ESA (without granulocyte-colony stimulating factor) and azacitidine. Seeing that CMML is a distinct disease entity, therapeutic strategies in CMML need to be tailored according to the specific features of CMML that includes both myelodysplastic as well as myeloproliferative characteristics. Therefore, international RCTs that are specifically designed for patients with CMML are warranted to more rapidly advance treatment strategies for these patients, which, in turn, will improve outcome in this rare malignancy that is associated with detrimental outcome without specific intervention. In addition, the value of CMML-specific scoring systems should be assessed in RCTs to ultimately provide evidence on the most appropriate prognostic model that can be used for risk-adapted treatment decision-making. Currently, none of the proposed scoring systems for CMML have as yet gained widespread acceptance like the IPSS for MDS.[68]

2.3 Effectiveness of azacitidine in routine clinical practice

Another purpose of the establishment of the PHAROS MDS registry was to perform comparative effectiveness research concerning azacitidine. In 2009, following the results of the pivotal phase 3 AZA-001 trial, azacitidine was temporarily approved in the Netherlands as an expensive pharmaceutical by the European Medicines Agency for the treatment of transplant-ineligible patients with higher-risk MDS.[32] As a result of the categorization of azacitidine as an expensive pharmaceutical, comparative effectiveness research is a requisite of the Dutch Health Care Institute, as they will decide, based on post-approval clinical and cost-effectiveness studies, whether future reimbursement for an expensive pharmaceutical will be continued, usually after 4 years since initial registration. In **chapter 7**, we specifically focused on the clinical effectiveness of azacitidine compared with BSC only and intensive chemotherapy for the treatment of transplant-ineligible patients with exclusively higher-risk MDS in the Netherlands. The cost-effectiveness of azacitidine was outside the scope of the current thesis.

In **chapter 7**, we showed in a population-based setting that azacitidine could prolong overall survival relative to BSC only, whereas overall survival between azacitidine-treated patients and patients who received intensive chemotherapy was similar. Azacitidine prolonged overall survival with 9.6 months relative to BSC only, which was strikingly similar to that observed in the AZA-001 trial, as it also prolonged overall survival with 9.6 months relative to BSC only.[32] However, azacitidine-treated patients in Dutch routine clinical practice had comparatively inferior overall survival compared with their counterparts recruited in the AZA-001 trial, namely a median overall survival

of 16.9 against 24.5 months. Similarly, overall survival of azacitidine-treated patients included in a large Spanish population-based study[79] as well as in a French patient-named compassionate program[80] was also generally poorer (median overall survival, 13.1 and 13.5 months, respectively). These differences may suggest that patients recruited in the AZA-001 trial may not be entirely representative of the general MDS population. Indeed, exclusion criteria of the AZA-001 trial prohibited patients with therapy-related MDS and those with an estimated life expectancy of less than 3 months to be entered on that trial.[32] Therefore, the effectiveness of recently approved pharmaceuticals should always be evaluated in the setting of routine practice to assess whether findings from clinical trials translate into benefits for patients in routine clinical practice.

Treatment recommendations for azacitidine in higher-risk MDS were established based on evidence provided by the AZA-001 trial.[22,81,82] In general, they recommend that azacitidine should be given for at least 6 cycles, as repeated azacitidine cycles are needed for a response to become apparent. In addition, azacitidine should be given to responders until disease progression or unacceptable toxicity occurs. In the study described in **chapter 7**, we showed that patients who did not responded to azacitidine received a median (range) of 5 (1-18) cycles, whereas responders received a median (range) of 13.5 (3-26) cycles, indicating that treatment recommendations were largely followed in Dutch routine clinical practice. In this regard, comparative effectiveness research is also suitable to assess whether the delivery of care to patients was provided according to treatment recommendations. For instance, a large population-based study that was conducted in Spain could not demonstrate a beneficial effect of azacitidine relative to BSC only and intensive chemotherapy. The most likely explanation might be the comparatively low treatment cycles given to patients in that study, namely a median of 6 cycles against 8.5 and 9 cycles in our population-based study (**chapter 7**) and the AZA-001 trial,[32] respectively. Therefore, caution should always be taken when interpreting results of population-based studies, as it is important to assess whether the care was delivered according to the treatment recommendations. Also, confounding by indication is a drawback in population-based studies, as the choice for a particular treatment approach is not based on randomization (i.e. poor internal validity). Nevertheless, that limitation does not make this type of research less valuable, as RCTs also have their own limitations (e.g. poor external validity).

Overall survival among transplant-ineligible patients with higher-risk MDS treated with either azacitidine or intensive chemotherapy does not seem to be different, as shown in the AZA-001 trial[32] as well as in several retrospective studies,[79] including our population-based study that is described in **chapter 7**. The AZA-001 trial was, however, limited by small patient numbers for that particular comparison, and, more importantly, not powered for that comparison. In addition, we noted in **chapter 7** that azacitidine-

treated patients spend substantial less days hospitalized for their treatment compared with patients who received intensive chemotherapy. One should keep in mind that azacitidine-treated patients and patients treated with intensive chemotherapy are entirely different populations. For example, in our study presented in **chapter 7**, patients who received intensive chemotherapy were significantly younger and had lesser comorbidities than those who received azacitidine. In the AZA-001 trial, patients who received intensive chemotherapy were also younger and had better performance status than patients who received azacitidine (information on comorbidity not reported).[32] The definitive answers whether azacitidine (or decitabine) is preferred over intensive chemotherapy for the treatment of patients with MDS who are not eligible for an alloHSCT needs to be demonstrated in a trial that is specifically designed and sufficiently powered to make that comparison. A phase 3 trial has recently been opened for accrual that specifically addresses the abovementioned question, albeit for newly diagnosed, untreated patients with AML aged 60 years or older, irrespective of transplant eligibility. That trial is designed under the auspices of the European Organization for Research and Treatment of Cancer (EORTC) and aims to assess the efficacy of frontline treatment with a 10-day decitabine schedule compared with standard intensive induction chemotherapy. A similar trial should also be specifically designed for patients with higher-risk MDS according to the WHO classification.

3. FUTURE PERSPECTIVE

3.1 Cancer registration in the Netherlands

Since its establishment in 1989, the nationwide population-based NCR, which is maintained and hosted by the Netherlands Comprehensive Cancer Organisation (IKNL), provides basic indicators relevant for cancer surveillance, namely incidence, prevalence, primary treatment and survival. In addition, the regional Eindhoven Cancer Registry, which is a part of the nationwide NCR, records information on comorbidity since 1993 for all patients diagnosed within the Eindhoven region (approximately 2.5 million inhabitants). However, additional parameters are needed across the entire NCR to evaluate more specific aspects concerning the quality of hemato-oncological care in its broadest sense. Therefore, since the incidence year 2014, based on the experience and knowledge gained through the PHAROS registry, the NCR has extended its nationwide registry by including a selected number of additional variables, also known as the NCR+. For instance, the additional variables for MDS in the NCR+ include several patient- (e.g. performance status and comorbidity) and disease-related characteristics (e.g. cytogenetics) at baseline, as well as more detailed information on treatment regimens

in first- and subsequent lines, along with the response to treatment. Furthermore, additional variables will also be standardly collected for CMML and AML, as well as other myeloid (e.g. CML) and lymphoid malignancies (e.g. non-Hodgkin lymphoma and multiple myeloma). Hematologists from several institutions across the Netherlands with specific knowledge on particular hematological malignancies—mostly representatives of cancer-specific HOVON working parties—were fully involved, along with epidemiologist from IKNL, to shape the NCR+ for hematological malignancies. Before the establishment of this extended registry, HOVON and IKNL were primarily working together in the field of clinical trials (e.g. IKNL provided services for local trial data management) and multidisciplinary consultations. At present, HOVON and IKNL consolidated their strengths to also work more closely together in the field of population-based research. As shown in this thesis, data from the regional PHAROS MDS registry and the nationwide NCR provided valuable insight into patient populations that can potentially be targeted for clinical trials. HOVON can use this information gained through population-based research to design specific clinical trials for patient populations that are currently excluded or underrepresented in current HOVON trials. In addition, information from the NCR+ can be utilized to evaluate whether clinical practice guidelines concerning diagnosis and treatment were followed. Whenever clinical practice guidelines are established or updated by HOVON, the NCR+ can adapt accordingly to incorporate novel indicators tailored to a specific hematological malignancy. Altogether, data from the NCR+ will provide valuable information in the near feature about the quality of hemato-oncological care in the Netherlands. Cooperation between HOVON and IKNL will thus be essential in the forthcoming years to monitor that care and to ensure that the quality of that care reaches and remains at the highest level.

In the meantime, the clinical epidemiology of hematological malignancies not studied in this thesis can be delineated with information from the minimal dataset of the NCR that currently spans over 25 years (i.e. incidence year from 1989 to 2013). Also, information on concomitant comorbidities at diagnosis that is recorded in the Eindhoven Cancer Registry can be interrogated to assess, for example, the impact of comorbidity on treatment decision-making and survival in hematologic malignancies. Furthermore, the NCR can be enriched with other databases/registries, such as the Achmea Health Database (AHD), which is a Dutch medical claims database that records payments for the delivery of all medical care to its insured population.[83] The coverage of the AHD is suggested to be representative for the urbanized areas of the Netherlands (approximately 1.2 million people). Although not nationwide, the AHD can provide more detailed data on treatment provisions than the DIS. Lastly, as for the regional PHAROS MDS registry, it can be utilized to address questions not considered in this thesis. For example, it would be interesting to investigate in-depth the application and outcome of ESA in MDS, especially in the light of the predictive model for response to ESA.[84,85]

3.1.1 Biobanking

The NCR, with its associated clinical and longitudinal follow-up data, can be linked to stored bone marrow specimens (e.g. specimens stored through the National String of Pearls Initiative—the Parelsnoer Initiative[86]) in order to advance translational cancer research, especially on biological characterization and prognosis.[87] Established in 2008, the Parelsnoer Initiative is a collaboration between eight university hospitals in the Netherlands that aims to support the advance of science, improve patient treatment and stimulate the development of novel products.[86] Bone marrow specimens from patients with hematological malignancies who are referred to university hospitals can be included in the Parelsnoer Initiative after they gave informed consent. Furthermore, the Parelsnoer Initiative was established to design an infrastructure for the collection of biospecimens from patients with hematological malignancies and other chronic diseases (e.g. inflammatory bowel diseases and diabetes mellitus). However, as shown in this thesis, the majority of patients with MDS, CMML and AML are diagnosed and managed in non-university hospitals, thereby they escape the attention of university hospitals, resulting in that the biological features of these patients remain ill-defined. In a similar fashion, RCTs also experience such selection bias, as biospecimens of the minority of older patients with MDS, CMML and AML that ultimately enter into RCTs may not be representative of the general older population. In this respect, a population-based cancer registry with an associated biobank is of particular interest to specifically investigate tumor biology and natural history of the disease in these patients at the population level, for which the latter is, in part, influenced by the presence of concomitant comorbidities and other health-related issues that are usually not present in younger patients with the same disease.

3.2 Cancer registration at the European level

The project Surveillance of Rare Cancers in Europe (RARECARE) defines a rare cancer as one with an annual crude incidence rate of less than 6 per 100,000 persons.[88] As a group, myeloid malignancies are a collection of comparatively rare tumors with an overall annual age-standardized incidence rate of 7.6 per 100,000 persons in Europe.[89] Within this spectrum—and under the definitions set by RARECARE—MDS, CMML and AML are rare malignancies. Most European countries have central cancer registries that either cover the entire nation or a well-defined geographic region. Even though cancer registries captures all newly diagnosed malignancies within a well-defined area, it might still be difficult to study the epidemiology of rare malignancies, especially when a cancer registry covers a region with relatively few inhabitants or when it was only recently established, any or all of which might result in comparatively small patient numbers to study meaningful epidemiological trends with statistical certainty. Therefore, the combination of multiple registries active at the European level will advance epidemiological

studies on rare malignancies by increasing patient numbers. In fact, an European cancer registry is already established, namely the EUROCARE cancer registry, which is a collection of 107 population-based cancer registries across European countries coalesced into one large European cancer registry.[90] The most recent update of the EUROCARE registry, that is, the EUROCARE-5 registry, contains around 22 million records of cancer patients diagnosed between 1978 and 2007,[90] including patients with hematological malignancies.[91] Epidemiological studies on very rare hematological malignancies is thus possible with data from the EUROCARE-5 registry.

Despite the high added value of this tremendous European cancer registry, they lack important clinical information on treatment, as well as on patient- and disease-related prognostic factors, which is not unexpected since it is not (financially) feasible to collect such data on a regular basis for all European countries. Data from the EUROCARE-5 cancer registry, which is primarily intended for cancer surveillance at the European level, only allows to assess trends in incidence and survival of malignancies across European regions (or countries). For example, a recent study with data from the EUROCARE-5 registry showed that survival of most patients with hematological malignancies at the population level increased steadily over time.[91] The improvement was most notable among younger patients, whereas improvement among elderly patients considerably lagged behind. The improvement in survival in that particular study could only be indirectly linked to increased application of particular treatment approaches over time. Therefore, representative samples of cancer registries across the whole of Europe are needed to collect additional clinical information, such as prognostic factors and treatment, to directly link them to improvements in survival. In fact, such registries are already active at the European level. A few examples are: the nationwide NCR+ for hematological malignancies—the successor of the regional PHAROS registry, the Düsseldorf MDS registry,[10] the European registry for lower-risk MDS (i.e. the EU-MDS registry),[92] the nationwide Swedish Acute Leukemia registry[26] and the nationwide Danish Acute Leukemia registry.[93] As MDS and AML are rare malignancies that are commonly not included in clinical trials, the ultimate aim would be to coalesce those registries into one large specialized European registry. Such a large registry will provide detailed clinical information to characterize these diseases more accurately at population level and may be part of evidence-based guideline development. To this end, we encourage these initiative across Europe and urge others to follow. In fact, the Swiss Group for Clinical Cancer Research (SAKK) is currently establishing a multicenter observational registry with an associated biobank for adult patients with MDS in Switzerland. Moreover, biospecimens linked to a cancer registry is already established in Sweden for patients with MDS. More specifically, all newly diagnosed patients with MDS from 2013 onwards that are included in the Swedish MDS registry can potentially be sampled for DNA. It is of great importance that biobanks established across Europe should combine their efforts to benefit the study of tumor biology among patients with hematological malignancies at the population level, especially for rare disorders such as MDS.

3.3 The best of both worlds: randomized controlled trials and population-based studies

The perils and merits of RCTs and population-based studies were discussed in this thesis. Despite the differences and tension between both research platforms, they should be regarded as complementary forms of research. The following proposal should contribute towards improved evidence-based medicine by using information gained from both RCTs and population-based studies. First of all, well-designed RCTs should assess the efficacy of novel therapies in order to identify a clinically significant benefit (e.g. as shown in the AZA-001 trial for azacitidine in higher-risk MDS[32]). Following the compelling findings of RCTs, treatment guidelines are established or updated (e.g. European LeukemiaNet[12] and HOVON guidelines for the treatment of MDS[22]). Subsequently, population-based studies should assess the uptake and effectiveness of novel interventions in routine clinical practice following the publication of pivotal RCTs and updated treatment guidelines (e.g. comparative effectiveness research on azacitidine described in **chapter 7**). Whenever findings from population-based studies demonstrate outcome congruent with findings from RCTs, it will support the use of a particular treatment approach in a wider population. However, whenever findings from RCTs do not translate into benefits for patients in routine clinical practice, population-based studies can identify gaps into the delivery of care and areas for improvement.

3.3.1 Comparative effectiveness research in a new lease of life

Pomalidomide was recently approved in the Netherlands following the results of a phase 3 clinical trial (i.e. the MM-003 trial) for the treatment of relapsed/refractory multiple myeloma (RRMM).[94] Like azacitidine for higher-risk MDS, pomalidomide is registered in the Netherlands as an expensive orphan drug. HOVON, the Dutch Society of Hematology (NVvH), IKNL, Celgene Netherlands (the manufacturer of pomalidomide) and particular health care insurance companies have made agreements regarding the prescription, reimbursement and costs of pomalidomide in the Netherlands, with the aim to guarantee access to pomalidomide in the coming time, especially for non-university hospitals. However, the reimbursement agreement for pomalidomide is different than the agreement for azacitidine (**chapter 9.2.3**). More specifically, in bilateral agreements made between Celgene Netherlands and several large health care insurance companies, the reimbursement and costs of pomalidomide are based on individual patient outcome, that is, the so-called 'pay-for-benefit' arrangement. This 'pay-for-benefit' arrangement is rather unique in the Netherlands, and, whenever proven to be useful in clinical

practice, may provide an example for others to follow. In order to assess patient outcome (e.g. treatment response) and whether pomalidomide was prescribed according to the most recent HOVON treatment guidelines for MM, agreements between HOVON and IKNL were made to register additional data in the NCR that are required to properly evaluate clinical effectiveness and guideline adherence. Of note, the NCR+ for hematological malignancies already collects data of patients with RRMM who were initially diagnosed with MM in the year 2014. After the inclusion of sufficient patients in the NCR, the effectiveness of pomalidomide (with low-dose dexamethasone) compared with high-dose dexamethasone alone for the treatment of patients with RRMM can be assessed.

3.3.2 Geriatric and health-related quality of life assessment

Treatment decisions in MDS, CMML and AML predominantly rely on prognostic models that primarily include disease-related characteristics.[21,66,68,95,96] However, it has been shown that patient-related characteristic such as comorbidities negatively influences prognosis, independent of disease-specific prognostic factors.[76,97] Comorbidities are currently only included in transplant prognostication, namely in the hematopoietic cell transplantation-specific comorbidity index (HCT-CI).[98] The HCT-CI is commonly used to predict the likelihood of non-relapse mortality and overall survival in patients with hematological malignancies receiving alloHSCT.[12,99] However, seeing that most patients with MDS, CMML and AML are predominantly diagnosed in a geriatric population (and thus are not eligible for an alloHSCT), additional scoring systems are needed to guide clinical management in this geriatric population, which should include all areas of health relevant to older patients. In this case, a comprehensive geriatric assessment (CGA) can identify problems within several health-related domains such as functional, social, nutritional and mental impairments that cannot be identified by prognostic models solely based on disease-related characteristics. A CGA may identify older, often frail patients who are most vulnerable to the toxicities of intensive therapy as well as older patients that likely will tolerate, and benefit from, intensive therapy.[100-104] Also, CGA may offer independent prognostic value to predict outcome after a specific intervention. Next to CGA, health-related quality of life (HRQoL) assessments may also be of value to assess domains of physical and psychological health, as well as social and role functioning. It has been demonstrated that pre-treatment HRQoL assessment may confer independent prognostic value to predict survival in patients with MDS[102,105] and AML,[102] as well as in patients with solid malignancies.[106-108] The ultimate aim is thus to incorporate specific CGA and HRQoL parameters into well-established disease-related prognostic models so it can be an integral part of the diagnostic work-up of older patients with MDS, CMML and AML in order to more precisely predict prognosis and plan individualized treatment approaches in this geriatric population.

3.4 Comprehensive Cancer Networks in the Netherlands

Generally, every patient with a malignant disease in the Netherlands should count on optimal care that is specifically tailored to patient- and disease-related characteristics, as well as based on the latest scientific knowledge, irrespective of the hospital where the initial care process started. This is especially relevant for older, often comorbid patients, as it may be cumbersome for these patients to regularly travel to a hospital for appropriate care that is not close to home. For instance, decitabine is registered in the Netherlands for the treatment of patients with AML aged 65 years or older who are not eligible for intensive therapy. Treatment with decitabine, which should be given for five consecutive days every 4 weeks, can only be provided within the setting of university hospitals. However, seeing that most older patients with AML are diagnosed and managed in non-university hospitals, one might argue that the provision of decitabine should not be concentrated to university hospitals. Therefore, it may be desirable that hospitals within a particular geographic region should more closely collaborate with each other to optimize the provision of care to patients within their region. Moreover, instead of concentrating care to a specific center, all health care professionals within a particular region should be fully involved in the whole care process of the patient, the so-called 'Comprehensive Cancer Network' idea.[109] In the field of hematological malignancies in the Netherlands, cooperation at the regional level is already started more or less. For example, HOVON introduced an echelon classification in 2008 with the primary purpose to determine, based on objective quality criteria, which hospitals could participate in clinical trials initiated by HOVON. This classification recognizes four service levels, namely A through D. Level A hospitals comprise of all eight university hospitals in the Netherlands that can perform both autoHSCT and alloHSCT, whereas Level B hospitals can only perform autoHSCT. Of note, alloHSCT is one of the most complex treatment approaches in hemato-oncology and it is thus indisputable that alloHSCT should be concentrated to highly specialized centers (i.e. university hospitals). Level C hospitals can provide intensive treatment to patients that does not involve HSCT and/or provide follow-up care for patients after HSCT who are referred from Level A or B hospitals. As for Level D hospitals, they can only provide non-intensive therapy (e.g. outpatient administration of azacitidine). HOVON centers clinical trial participation, and patient care in general, around all eight university hospitals (Level A) and two large non-university hospitals (Level B) that provides clinical consultation for non-university hospitals (Level C and D) within their referral area. Level C and D hospitals can provide specific care within the setting of clinical trials, provided they have made agreements with Level A or B hospitals. In this way, consultation centers can offer support to non-university hospitals in their referral area regarding the care of patients. Strengthening such collaboration in the setting of a Comprehensive Center Network will ensure that a broad range of health care approaches will be available for patients within the region, ranging from non-intensive

treatment to intensive, often complex treatment. The HOVON echelon classification should be the foundation to establish such Comprehensive Cancer Networks.

4. CONCLUDING REMARKS

It became evident in this thesis that population-based cancer registries are of vital importance to provide data on incidence and survival of MDS, CMML and AML at the population level. In addition, they can provide data complementary to that from RCTs that usually addresses a rather selected patient population, provided that they are well-established, include relevant parameters, cover the target population with high accuracy, and have an accurate follow-up. The results described in this thesis provided a benchmark for incidence, diagnosis, treatment and survival of MDS, CMML and AML in the Netherlands. Future studies with data from the newly established nationwide NCR+ should provide insight whether clinical and registration practice changed following the results described in this thesis. Furthermore, many elements were not considered in this thesis, such as the impact of specific comorbid conditions on treatment decision-making and outcome, molecular diagnostics, as well as CGA and HRQoL assessments, and biobanking. In the near future, studies should focus on these unresolved aspects, in particularly among elderly patients with hematological malignancies.

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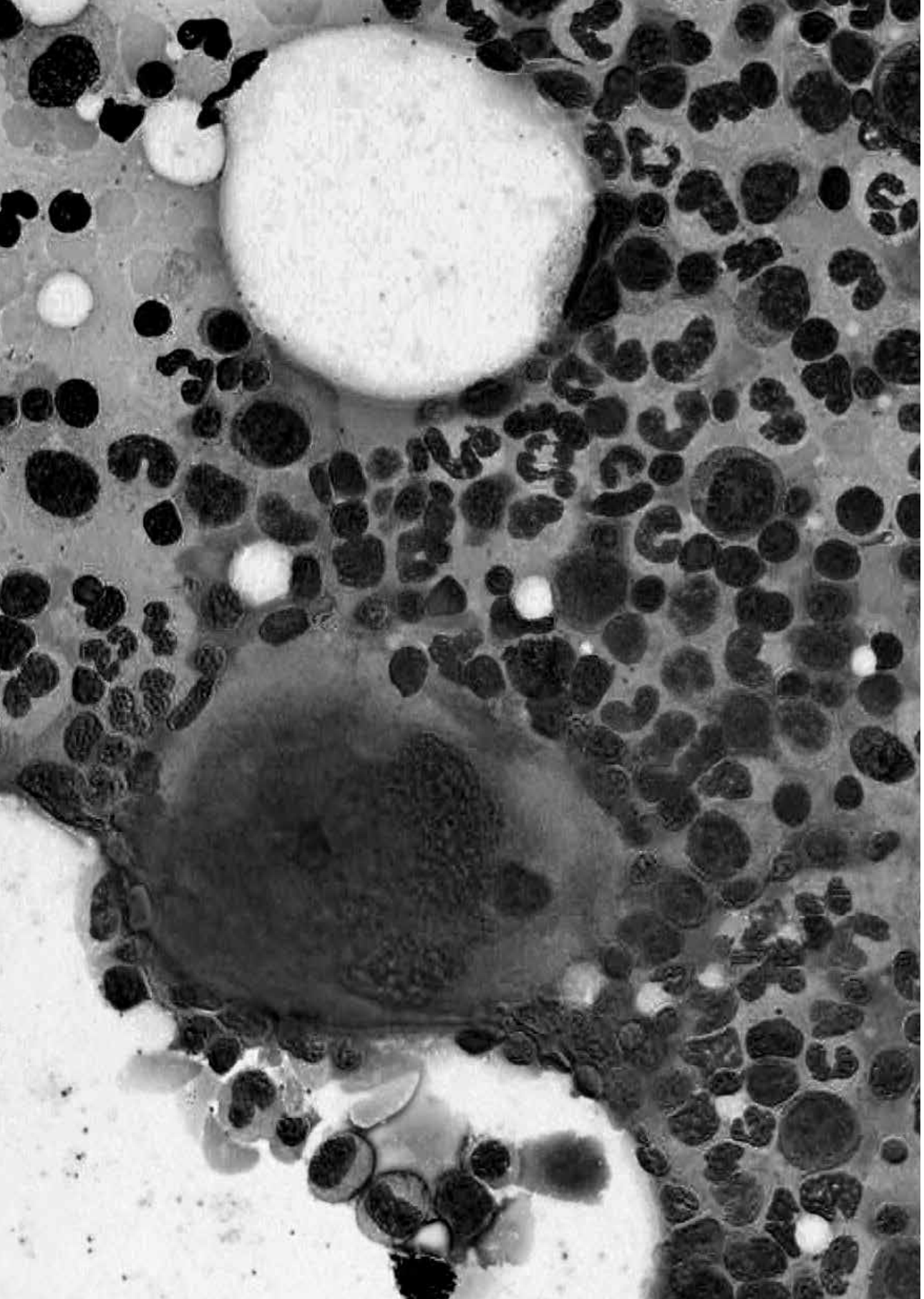

Addendum

Nederlandse samenvatting

INLEIDING

Hematologische maligniteiten zijn kankers van het beenmerg en de lymfeklieren en vormen ongeveer 8% van alle kankers die jaarlijks in Nederland worden gediagnosticeerd. Ongeveer 60% van de patiënten met hematologische maligniteiten zijn boven de 65 jaar ten tijde van de diagnose, hoewel de leeftijdsverdeling per diagnose kan variëren. Gezien de vergrijzing van de bevolking in Nederland zal het aantal oudere patiënten met hematologische maligniteiten de komende jaren aanzienlijk toenemen.

Myelodysplastische syndromen (MDS), chronische myelomonocytaire leukemie (CMML) en acute myeloïde leukemie (AML) zijn kankers van het beenmerg die het meest voorkomen bij patiënten boven de 65 jaar. Al deze vormen van beenmergkanker hebben gemeen dat ze hun oorsprong vinden in de myeloïde stamcel. Myeloïde stamcellen kunnen onder invloed van specifieke groeifactoren in het beenmerg uitrijpen (differentiëren) tot functionele bloedcellen, te weten: rode bloedcellen (erytrocyten), verschillende witte bloedcellen (zoals granulocyten) en bloedplaatjes (trombocyten). Verworven mutaties in het DNA van myeloïde stamcellen kunnen verstoringen veroorzaken in het differentiatieproces van deze stamcellen, met als gevolg dat ze inadequaat tot uitrijping komen als functionele cellen.

MDS en CMML vormen een heterogene scala van beenmergstoornissen die worden gekenmerkt door ten minste 1 cytopenie in het perifere bloed, dysplasie van ten minste 1 cellijn in het beenmerg en hoogstens 20% blasten in het beenmerg en/of perifeer bloed. Daarnaast hebben beide ziektebeelden een tendens om over te gaan naar AML. Deze kenmerken zijn allemaal uitingen van ineffectieve hematopoëse waaraan een klonale afwijking van de myeloïde stamcel ten grondslag ligt. Bij MDS en CMML leidt dit tot vroegtijdig celdood in het beenmerg waardoor er een tekort aan functionele cellen ontstaat in het perifeer bloed. Bij AML leidt ineffectieve hematopoëse tot een woekering (proliferatie) van onrijpe witte bloedcellen in het beenmerg, met als gevolg dat de aanmaak van functionele cellen vrijwel verdrongen is.

De diagnostiek van MDS, CMML en AML omvat verschillende onderdelen waarbij het bloed-, cytomorfologisch-, histopathologisch-, immuunfenotypisch- en cytogenetisch onderzoek centraal staan. Deze onderzoeken zijn noodzakelijk om een classificerend subtype toe te kennen, omdat elk type hematologische maligniteit onderverdeeld kan worden in een specifieke entiteit. Uitkomsten van diagnostische verrichtingen worden, naast het classificeren van het ziektebeeld, ook gebruikt in prognostische modellen om het risicoprofiel voor de individuele patiënt te bepalen. Het risicoprofiel geeft een inschatting over de te verwachten levensverwachting (prognose) en, samen met de leeftijd van de patiënt en comorbiditeit, richting aan de therapiekeuze. De behandeling van hematologische maligniteiten bestaat uit vele modaliteiten, zoals ondersteunende zorg,

immuunmodulerende middelen, doelgerichte therapie, intensieve en laag-gedoseerde chemotherapie, alsmede hematopoëtische stamceltransplantatie (HSCT).

GERANDOMISEERDE KLINISCHE STUDIES EN OBSERVATIONELE STUDIES

Gerandomiseerde klinische studies zijn essentieel om nieuwe diagnostische technologieën en behandelingen te evalueren. Op basis van resultaten die voortkomen uit gerandomiseerde klinische studies worden richtlijnen voor de dagelijkse klinische praktijk ontwikkeld. Hierin wordt vastgesteld wat het belang is van adequate diagnostiek en behandeling die afgestemd is op het individueel risicoprofiel. Klinische studies zijn doorgaans onderhevig aan strikte inclusie- en exclusiecriteria. In de meeste gevallen zijn oudere patiënten (met comorbiditeit) ruim ondervertegenwoordigd in klinische studies, hetgeen leidt tot een geselecteerde patiëntenpopulatie in zulke studies. Aanbevelingen over de diagnostiek en behandeling van oudere patiënten zijn meestal niet evidence-based, met mogelijk variatie in diagnostiek en behandeling als gevolg. Gerandomiseerde klinische studies kunnen gecomplementeerd worden met gegevens afkomstig uit populatie-gebaseerde registraties om aanbevelingen over de diagnostiek en behandeling in de dagelijkse klinische praktijk te ondersteunen. Daarnaast kunnen zulke registraties bijdragen aan het optimaliseren van de kwaliteit van de hemato-oncologische zorg in de breedste zin van het woord. Het primaire doel van een population-based kankerregistratie is om de omvang van de kankerlast te bepalen en de evolutie ervan te beoordelen in een bepaald geografisch gebied. Derhalve is een population-based kankerregistratie een goed instrument om alle patiënten te besturen binnen een afgebakend gebied, aangezien deze niet de beperkingen heeft zoals strikte inclusie- en exclusiecriteria van gerandomiseerde klinische studies.

DOEL VAN DIT PROEFSCHRIFT

Gezien de beperkte hoeveelheid aan beschreven population-based onderzoek naar MDS, CMML en AML in Nederland, is het doel van dit proefschrift om de kennis te verhogen over verschillende epidemiologische aspecten van deze ziektebeelden in Nederland. Deze aspecten omvatten kankersurveillance om de omvang van de kankerlast te bepalen en de evolutie ervan te beoordelen, toepassing van diagnostische en therapeutische strategieën, adherentie aan richtlijnen ten aanzien van diagnostiek en behandeling en onderzoek naar klinische effectiviteit van therapeutische interventies die worden

toegepast bij patiënten in de dagelijkse praktijk. Het onderzoek dat beschreven is in dit proefschrift maakt gebruik van drie Nederlandse databanken om de klinische epidemiologie van MDS, CMML en AML uiteen te zetten, namelijk (i) de landelijk dekkende Nederlandse Kankerregistratie (NKR), (ii) het landelijk DBC-informatiesysteem en (iii) de Nederlandse PHAROS registratie (**P**opulation-based **HA**ematological **R**egistry for **O**bservational **S**tudies) voor patiënten met MDS en CMML—de PHAROS MDS registry.

BELANGRIJKSTE BEVINDINGEN VAN DIT PROEFSCHRIFT

Onderzoek met gegevens uit de Nederlandse Kankerregistratie

In **hoofdstukken 2 tot en met 4** hebben wij de klinische epidemiologie van MDS, CMML en AML in Nederland uiteengezet, gebruikmakend van de landelijk dekkende NKR. De NKR verzameld sinds 1989 op landelijk niveau de voornaamste karakteristieken, zoals algemene demografische en klinische gegevens, van alle kankerpatiënten in Nederland. Sinds 2001 worden ook alle gevallen van MDS en bepaalde myeloproliferatieve neoplasieën opgenomen in de NKR. In **hoofdstuk 2** beschreven wij trends in vóórkomen (incidentie), primaire behandeling (eerstelijnsbehandeling) en relatieve overleving van patiënten met een MDS die tussen 2001 en 2010 werden gediagnosticeerd in Nederland. De relatieve overleving is een benadering van de ziektespecifieke overleving en wordt berekend als de ratio van de waargenomen overleving in een patiëntenpopulatie en de verwachte overleving van een naar leeftijd en geslacht vergelijkbare populatie in de algemene bevolking. Met andere woorden; de overlevingcijfers van patiënten worden gecorrigeerd voor de levensverwachting van de algemene bevolking. Het naar leeftijd gestandaardiseerd incidentiecijfer per 100.000 personen per jaar steeg van 2,3 in de periode 2001-2005 naar 2,8 in de periode 2006-2010 en bleef sedert 2007 stabiel rond 2,8. De incidentie van MDS steeg vermoedelijk als gevolg van een beter bewustzijn van het ziektebeeld, alsmede verbeterde registratie in de NKR, in plaats van veranderingen in etiologische oorzaken. De mediane leeftijd bij diagnose was 74 jaar en 66% van de patiënten was 70 jaar of ouder. De leeftijdsspecifieke incidentie van MDS steeg aanzienlijk met toenemende leeftijd en was het hoogst in de leeftijdscategorie 80 jaar of ouder (32,1 per 100.000 personen per jaar in de periode 2006-2010). Het aandeel patiënten met een MDS dat geen subclassificatie kreeg daalde van 60% in 2001 naar 36% in 2010. Dit resultaat suggereert dat hematologen, morfologen en pathologen in de loop van de tijd steeds meer vertrouwd raakten met het vernieuwde classificatiesysteem van MDS dat in 2001 werd geïntroduceerd. Het leeuwendeel van de patiënten (89%) kreeg geen eerstelijnsbehandeling binnen zes maanden na diagnose. Er was geen verschil in percentages wat betreft de toegepaste eerstelijnsbehandelingen door de tijd.

De relatieve overleving van patiënten met een MDS nam af met toenemende leeftijd en verbeterde nagenoeg niet gedurende de gehele observatieperiode van 2001-2010. De relatieve vijfjaarsoverleving van patiënten met MDS in de leeftijdscategorie 18-49, 50-59, 60-69, 70-79 en 80 jaar of ouder bedroeg, respectievelijk, 59, 52, 41, 36 en 29% in de periode 2001-2010. Het beperkte arsenaal aan geneesmiddelen voor de behandeling van MDS, alsmede de terughoudendheid ten aanzien van het behandelen van patiënten met een MDS, kunnen deels geleid hebben tot het ontbreken van een verbetering in de overleving.

In **hoofdstuk 3** beschreven wij trends in incidentie, eerstelijnsbehandeling en relatieve overleving van patiënten met CMML die tussen 1989 en 2012 werden gediagnosticeerd in Nederland. CMML is een zeer zeldzame hematologische kanker die voornamelijk bij oudere personen voorkomt. Het jaarlijks naar leeftijd gestandaardiseerd incidentiecijfer per 100.000 personen steeg gestaag met de tijd, maar bleef sedert 2008 stabiel rond 0,4 per 100.000 personen per jaar. De mediane leeftijd bij diagnose was 76 jaar in de meest recente observatieperiode van 2007-2012. De toepassing van chemotherapie als eerstelijnsbehandeling nam af met toenemende leeftijd, terwijl HSCTs slechts in 5% van patiënten in de leeftijdscategorie 70 jaar of jonger werd toegepast. De toegepaste eerstelijnsbehandeling, alsmede de relatieve overleving, bleven in de afgelopen decennia nagenoeg onveranderd. De relatieve vijfjaarsoverleving van patiënten met CMML was indrukwekkend laag voor alle leeftijdscategorieën, namelijk 21, 23, 20 en 12% voor, respectievelijk, de leeftijdscategorieën 18-59, 60-69, 70-79 en 80 jaar of ouder. De slechte prognose die onveranderd bleef over de tijd kan deels toe te schrijven zijn aan het gebrek van geneesmiddelen die specifiek ontworpen zijn voor CMML. Dit aangezien vrijwel alle therapeutische modaliteiten die beschikbaar zijn voor patiënten met dit ziektebeeld zijn geëxtrapoleerd van de kennis en kunde die is op gedaan bij de behandeling van patiënten met een MDS.

In **hoofdstuk 4** onderzochten wij behandeling, studiedeelname en relatieve overleving van patiënten met AML die in Nederland tussen 1989 en 2012 werden gediagnosticeerd. De toepassing van allogene HSCT (alloHSCT) bij patiënten met AML in de leeftijdscategorie onder de 70 jaar nam met de tijd toe, terwijl patiënten in de leeftijdscategorie boven de 70 jaar voornamelijk ondersteunende zorg kregen. Ongeveer 60% van de patiënten in de leeftijdscategorie onder de 60 jaar kreeg zijn/haar behandeling in het kader van een klinische studie. Desondanks AML een ziekte is die voornamelijk bij personen boven de 60 jaar voorkomt—de mediane leeftijd bij diagnose was 68 jaar in de periode 2007-2012—was de studiedeelname bij deze leeftijdscategorie disproportioneel laag. Het percentage studiedeelname bij patiënten in de leeftijdscategorie 61-70 en boven de 70 jaar was, respectievelijk, 30 en 12%. De relatieve overleving van patiënten met AML steeg gestaag over de laatste twee decennia, echter alleen voor de leeftijdscategorie tot en met 70 jaar. De relatieve vijfjaarsoverleving voor patiënten met AML in de leeftijdscategorie 18-40, 41-60, 61-70 en boven de 70 jaar was, respectievelijk, 54, 38, 14 en 2% in de periode 2007-2012. In dit onderzoek werd apart gekeken naar patiënten met acute promyelocyten leukemie (APL). Dit ziektebeeld wordt gezien als een specifieke entiteit binnen de groep van AML vanwege zijn onderscheidende biologische, moleculaire en klinische karakteristieken alsmede manier van behandelen middels doelgerichte therapie, te weten met intensieve chemotherapie en retinoïnezuur (ATRA). Zowel de toepassing van chemotherapie bij alsmede de relatieve overleving van APL steeg in de afgelopen decennia voor alle leeftijdsgroepen. De relatieve vijfjaarsoverleving voor patiënten met APL in de leeftijdscategorie 18-40, 41-60, 61-70 en boven de 70 jaar bedroeg, respectievelijk, 84, 75, 54 en 37% in de periode 2007-2012. De relatieve overleving steeg het sterkst voor patiënten in de leeftijdscategorie boven de 60 jaar. Samenvattend bleek uit dit onderzoek dat de behaalde overlevingswinst van de afgelopen decennia hoogstwaarschijnlijk toegeschreven kan worden door het intensiever behandelen van patiënten met AML en APL in alle leeftijdscategorieën, met uitzondering van patiënten met AML boven de 70 jaar. Voorts moeten er klinische studies beschikbaar komen voor patiënten met AML die niet in aanmerking komen voor behandeling in huidige klinische studies, aangezien ook voor deze patiënten behandelingen en uitkomsten bevorderd moeten worden, met name, maar niet uitsluitend, voor de leeftijdsgroep boven de 70 jaar.

Onderzoek met gegevens uit het landelijk DBC-informatiesysteem

Uit onderzoek dat werd uitgevoerd met gegevens afkomstig uit databanken van de gedeclareerde zorg in de Verenigde Staten van Amerika en Australië, bleek dat de kankerregistraties van die landen mogelijk een onderrapportage hebben van MDS en andere myeloïde maligniteiten. In **hoofdstuk 5** onderzochten wij of de NKR mogelijk ook een onderrapportage had van MDS en CMML in de periode tussen 2008 en 2010. Voor dit onderzoek hebben wij gebruik gemaakt van het landelijk dekkende **D**iagnose Behandeling Combinatie (DBC)-**i**nformatie**s**ysteem (DIS). Het DIS ontvangt en beheert alle gegevens omtrent afgesloten DBC-trajecten in onder andere de ziekenhuiszorg. DBC-trajecten omvatten alle verrichtingen ten aanzien van de geleverde zorg die vervolgens worden gedeclareerd. De diagnoses van MDS en CMML in het DIS werden in bijna de helft van de patiënten afgegeven zonder beenmergonderzoek, ondanks het feit dat het beenmergonderzoek noodzakelijk is om de diagnose van deze ziektebeelden vast te stellen dan wel uit te sluiten. Het uitvoeren van een beenmergonderzoek nam sterk af met toenemende leeftijd. Het naar leeftijd gestandaardiseerd incidentiecijfer van MDS in het DIS was bijna twee keer zo hoog vergeleken met recente incidentiecijfers van de NKR, namelijk 5,4 tegenover 3,3 per 100.000 personen per jaar in de periode 2008-2010. De incidentiecijfers bleken echter vergelijkbaar te zijn wanneer de gevallen zonder

het beenmergonderzoek uit het DIS buiten beschouwing werden gelaten, namelijk 3,0 tegenover 3,3 per 100.000 personen per jaar in de periode 2008-2010. Deze resultaten suggereren dat de NKR mogelijk geen onderrapportage had van MDS in de periode 2008-2010. De incidentie van CMML bleek daarentegen hoger te zijn in het DIS dan in de NKR, namelijk 0,2 tegenover 0,4 per 100,000 personen per jaar in de periode 2008-2010. Een verklaring hiervoor is echter niet eenvoudig te vinden, aangezien de NKR gevallen van CMML registreerd die door de arts zijn bevestigd middels het histopathologisch en/of cytomorfologisch onderzoek.

Onderzoek met gegevens uit de PHAROS MDS registratie

De studies die werden beschreven in **hoofdstukken 2 en 3** leverden belangrijke informatie over epidemiologische aspecten van MDS en CMML in Nederland, gebaseerd op gegevens van de landelijk dekkende NKR. De NKR vormt de basis voor kankersurveillance in Nederland en is derhalve een goed instrument om de omvang van de kankerlast te bepalen en de evolutie ervan te beoordelen. Gegevens uit de NKR zijn echter niet toereikend om specifiekere analyses te verrichten om in detail inzicht te krijgen in toegepaste diagnostische (zoals het cytogenetisch onderzoek) en therapeutische strategieën (zoals het gebruik van azacitidine) alsmede in uitkomsten van diagnostiek (zoals prognose volgens de **I**nternational **P**rognostic **S**coring **S**ystem—IPSS) en behandeling (zoals respons op azacitidine). De PHAROS MDS registry is een population-based, hemato-oncologische registratie die de bovenstaande en andere relevante gegevens wel verzamelen. De PHAROS MDS registry is in feite een uitbreiding van de NKR, aangezien er additionele gegevens worden verzameld naast de standaard dataset van de NKR. De PHAROS MDS registry is echter niet landelijk dekkend, maar dekt ongeveer 40% van Nederland, namelijk de regio's Rotterdam en Amsterdam. In **hoofdstuk 6 en 7** werd de geleverde zorg aan patiënten met MDS en CMML in kaart gebracht, gebruikmakend van de PHAROS MDS registry, om zo de kwaliteit van de diagnostiek en behandeling van MDS en CMML in de dagelijkse klinische praktijk te bevorderen.

In **hoofdstuk 6** onderzochten wij hoe de richtlijn omtrent diagnostiek en behandeling van MDS en CMML werd toegepast in de dagelijkse klinische praktijk, om zo valide uitspraken te kunnen doen over de geleverde zorg. In dit onderzoek werd het accent gelegd op het beenmerg- en cytogenetisch onderzoek, omdat deze onderdelen, in combinatie met het bloedonderzoek, centraal staan om volgens de IPSS het individueel risicoprofiel van een patiënt met MDS te bepalen. De IPSS kan vier risicogroepen onderscheiden, te weten: laag (0 punten), intermediar-1 (0,5-1,0 punten), intermediar-2 (1,5-2,0 punten) en hoog risico (≥2,5 punten). Het risicoprofiel geeft een inschatting over de te verwachte prognose en geeft daarnaast richting aan de therapiekeuze. Voor CMML is er momenteel geen klinische richtlijn beschikbaar, maar is wel in ontwikkeling onder de auspiciën van de werkgroep AML/MDS van de Stichting Hemato-Oncologie voor Volwassenen in Nederland (HOVON). Advies ten aanzien van de diagnostiek en behandeling van CMML wordt momenteel geëxtrapoleerd van MDS. Uit dit onderzoek bleek dat een groot aandeel van patiënten met MDS en CMML niet volledig volgens de richtlijn werd gediagnosticeerd. Het percentage dysplasie in de erytroïde, granulocytaire en megakaryocytaire reeks van het beenmerg was in, respectievelijk, 33, 34 en 30% van de gevallen gerapporteerd, ondanks het beenmergaspiraat evalueerbaar was in vrijwel alle patiënten met MDS en CMML. Voorts was het percentage blasten in evalueerbare beenmergmonsters niet bekend in 17% van de gevallen. Het beoordelen van morfologische kenmerken in het beenmerg (zoals het percentage dysplasie en blasten in het beenmerg) is belangrijk voor de classificatie en prognosticatie. Daarnaast bleek dat het cytogenetisch onderzoek niet werd uitgevoerd in bijna de helft van patiënten met MDS (46%) en CMML (42%). Een risicoprofiel volgens de IPSS kon niet worden toegewezen aan bijna de helft van patiënten met een MDS, omdat met name het cytogenetisch onderzoek niet werd uitgevoerd in bijna de helft van de patiënten. Het niet volledig kunnen berekenen van een IPSS score kan potentieel leiden tot inadequate klinische besluitvorming. Uit een analyse met behulp van multivariabele logistische regressie kwam naar voren dat oudere leeftijd, twee of meer comorbiditeiten bij diagnose, diagnose in een niet-academisch centrum en geen behandeling voor een kanker in de voorgeschiedenis geassocieerd zijn met terughoudendheid ten aanzien van het uitvoeren van cytogenetisch onderzoek. De richtlijn voor de behandeling van MDS beveelt over het algemeen aan om symptomatische patiënten met laag-risico MDS volgens de IPSS (te weten: laag of intermediar-1 risico) te behandelen met erytropoieitine (EPO) om bloedarmoede (anemie) te corrigeren, terwijl patiënten met hoog-risico MDS volgens de IPSS (te weten: intermediair-2 of hoog risico) in aanmerking komen voor curatieve behandeling (te weten: allogene HSCT al dan niet voorafgaand intensieve chemotherapie) of, indien curatieve behandeling geen haalbare kaart is, azacitidine. Ondanks deze richtlijn bleek uit dit population-based onderzoek dat een aantal patiënten met laag-risico MDS behandeld werden met azacitidine, een middel dat alleen voor hoog-risico MDS geïndiceerd is, en dat een aantal patiënten met hoog-risico MDS behandeld werden met EPO, een modaliteit die nauwelijks effectief is in deze risicogroep. Uit een multivariabele logistische regressie analyse bleek overigens dat oudere leeftijd, slechte performance status, een onvolledige IPSS score en diagnose in een niet-academisch centrum geassocieerd zijn met terughoudendheid ten aanzien van behandeling met antineoplastische modaliteiten (te weten: alloHSCT, intensieve chemotherapie, azacitidine en hydroxyurea). Multivariabele analyses zoals voorgaand beschreven voor cytogenetisch onderzoek bij en behandeling van MDS werden niet uitgevoerd voor CMML, aangezien het aantal patiënten met CMML te klein waren in verschillende categorieën om robuuste uitspraken te kunnen doen met een zekere graad

van (statistische) betrouwbaarheid. Toekomstige studies met gegevens afkomstig uit Nederlandse population-based registraties, zoals de PHAROS MDS registry, zullen nodig zijn om uit te wijzen of de richtlijn omtrent diagnostiek en behandeling van MDS en CMML beter gevolgd wordt.

In **hoofdstuk 7** onderzochten wij de klinische effectiviteit van azacitidine ten opzichte van ondersteunende zorg en intensieve chemotherapie voor de behandeling van patiënten met hoog-risico MDS in Nederland die niet in aanmerking komen voor een HSCT. De mediane overleving van patiënten die werden behandeld met azacitidine, ondersteunende zorg en intensieve chemotherapie was, respectievelijk, 14,6, 7,3, en 14,3 maanden na start van therapie. Uit een multivariabele Cox regressie analyse bleek dat behandeling met azacitidine was geassocieerd met betere overleving ten opzichte van ondersteunende zorg, terwijl er tussen azacitidine en intensieve chemotherapie geen verschil was in overleving. Patiënten die werden behandeld met intensieve chemotherapie werden echter langer klinische opgenomen dan patiënten die met azacitidine werden behandeld (mediaan aantal opnamedagen: 71 tegenover 2.5). Alle patiënten die met azacitidine werden behandeld kregen over het algemeen mediaan 8,5 kuren azacitidine toegediend. Patiënten die enige respons vertoonde op azacitidine hadden een betere overleving dan patiënten waarbij geen respons optrad; zij kregen respectievelijk mediaan 13,5 en 5 kuren azacitidine toegediend. Samenvattend kwam uit dit onderzoek dat de klinische effectiviteit van azacitidine in de dagelijkse praktijk in Nederland, in termen van verlening van overleving en het aantal gegeven kuren, vergelijkbaar was met de resultaten van de fase 3 klinische studie (te weten de AZA-001 trial) die heeft geleidt tot de registratie van azacitidine in Nederland. Desalniettemin verging het patiënten uit de dagelijkse klinische praktijk slechter qua overleving dan hun tegenhangers in de AZA-001 trial, hetgeen suggereert dat patiënten die gerekruteerd worden voor klinische studies niet altijd een evenwichtige weerspiegeling zijn van patiënten in de algemene bevolking.

CONCLUDERENDE OPMERKINGEN

In het laatste **hoofdstuk 8** werden de meest belangrijkste bevindingen van het proefschrift in een ruimer context besproken en werden er aanbevelingen gedaan voor toekomstig onderzoek.

Het werd duidelijk uit de onderzoeken in dit proefschrift dat population-based registraties van vitaal belang zijn om inzicht te verschaffen in de incidentie, diagnostiek, behandeling en overleving van patiënten met MDS, CMML en AML in de algemene bevolking. Daarnaast kunnen zulke registraties als een geschikt platform dienen om gerandomiseerde klinische studies te complementeren, mits ze goed zijn opgezet,

relevante gegevens verzamelen, de omvang van de populatie nauwkeurig behelzen en zeer accuraat de vitale status van patiënten kunnen volgen. De resultaten die beschreven werden in dit proefschrift kunnen als een vergelijkingsmaatstaf (benchmark) dienen voor toekomstig onderzoek naar de incidentie, diagnostiek, behandeling en overleving van MDS, CMML en AML in Nederland. Voor alle hematologische maligniteiten worden sinds het diagnosejaar 2014 additionele gegevens verzameld in de landelijk dekkende NKR. De PHAROS registry behelst zodoende het hele land en is tegenwoordig ook bekend als de NKR+ voor hematologische maligniteiten dan wel het Nederlands hemato-oncologie register. De PHAROS registry heeft aan de basis gestaan voor het opzetten van de NKR+, aangezien de NKR+ mede door de kennis en kunde van de PHAROS registry is opgezet. Toekomstige studies met gegevens afkomstig uit de NKR+ zullen uitwijzen of zowel de klinische praktijk alsmede registratieaspecten omtrent MDS, CMML en AML positief zullen veranderen naar aanleiding van dit proefschrift.

GEBRUIKTE AFKORTINGEN

AML	Acute myeloïde leukemie
APL	Acute promyelocyten leukemie
ATRA	Retinoïnezuur (*all-trans retoinic acid)*
CMML	Chronische myelomonocytaire leukemie
DBC	Diagnose Behandeling Combinatie
DIS	DBC-informatiesysteem
HSCT	hematopoëtische stamceltransplantatie
MDS	Myelodysplastische syndromen
NKR	Nederlandse Kankerregistratie
PHAROS	**P**opulation-based **HA**ematological **R**egistry for **O**bservational **S**tudies

Dankwoord

LECTORI SALUTEM

Na vier jaar kan ik met veel trots terugkijken op een uiterst interessante en leerzame promotietijd. Ten einde van dit proefschrift wil ik graag een aantal mensen persoonlijk bedanken die hebben bijgedragen aan dit proefschrift, zowel direct als indirect. Alvast mijn welgemeende excuses als ik mensen niet heb opgenoemd in het hiernavolgende. Dit betekent echter niet dat ik je steun, op welke manier dan ook, niet heb gewaardeerd tijdens mijn promotietraject.

Zo begin ik traditioneel gewijs met het danken van mijn promotoren, te weten **prof. dr. Pieter Sonneveld** (1e promotor) en **prof. dr. Arjan van de Loosdrecht** (2e promotor). Beste **Pieter**, ik kan mijn sollicitatiegesprek met jou, inmiddels ruim 4 jaar geleden, nog erg goed herinneren. Je was namelijk enigszins bevreesd dat ik het promotieonderzoek saai zou vinden, aangezien ik destijds meer affiniteit had met laboratoriumonderzoek dan met epidemiologisch onderzoek. De afgelopen vier jaar zijn alles behalve saai geweest tijdens mijn promotietraject. Ik wil je bedanken voor het vertrouwen die je in mij had om het onderzoek bij jou op de afdeling te kunnen uitvoeren. Voorts wil ik je bedanken dat jij—als afdelingshoofd van de afdeling Hematologie van het Erasmus MC—mij de mogelijkheid hebt gegeven om een deelaanstelling te behouden bij jou op de afdeling.

Beste **Arjan**, jij was samen met Mojca aangewezen als mijn copromotor. Dit bleek echter van korte duur, aangezien jij in april 2013 hoogleraar werd en dus automatisch ook promotor. Ik denk dat wij een schoolvoorbeeld zijn, dat laat zien dat 'Rotterdammers' en 'Amsterdammers' tamelijk goed met elkaar kunnen samenwerken. Ondanks we elkaar infrequent ontmoette vanwege onze 'long-distance work relationship', waren de ontmoetingen altijd erg gezellig, maar vooral erg leerzaam. Hoewel het meeste contact verliep per mail of telefoon, reageerde je nagenoeg altijd erg vlot op mijn e-mails, met name als er naar een manuscript van mij gekeken moest worden. Als ik het toch heb over manuscripten, dan denk ik aan een aantal momenten waar Mojca en ik je waarschijnlijk enigszins op je zenuwen hebben gewerkt. Het ging vooral om enkele momenten waarop ik per mail aan jou en aan andere medeauteurs kenbaar maakte dat ik reeds gereviseerde manuscripten niet meer aan jullie voorleg voor review, maar direct zou aanbieden bij een tijdschrift en dat Mojca met deze gang van zaken instemt. Mojca en ik hebben inmiddels van jou geleerd dat we dit soort acties niet al te vaak moeten uitproberen, derhalve dat je vrijwel per omgaande reageert op verzoeken wat betreft het (her)beoordelen van manuscripten. Ik wil je bedanken voor je begeleiding, je aanstekelijke enthousiasme, de fijne samenwerking, en je geduld en vertrouwen in mij. Ik kijk in ieder geval erg uit naar onze toekomstige samenwerking omtrent population-based onderzoek naar myelodysplastische syndromen (MDS) op zowel nationaal als internationaal niveau.

Nu ik mijn promotoren heb bedankt, wil ik in het bijzonder een aantal woorden richten aan mijn copromotor, **dr. Mojca Jongen-Lavrencic**. Beste **Mojca**, ik durf met alle zekerheid te zeggen dat dit onderzoek niet zo succesvol was geweest, als ik jou niet had als dagelijkse begeleider. Andersom ook niet, als jij een andere promovendus had op dit onderzoek. Mijn promotietraject liet zien dat tegenslagen—in de breedste zin van het woord—positief kunnen uitpakken, mits je dynamisch van koers wisselt daar waar er obstakels opdoemen. Derhalve was mijn promotietijd, naast een wetenschappelijke uitdaging, ook een organisatorische (en deels een politieke) uitdaging. Kortom, ik had mij geen andere en betere dagelijkse begeleider kunnen voorstellen. Je hebt me doorgaans de ruimte gegeven om mijn eigen richting te kiezen binnen mijn promotieonderzoek. Ik ben daar erg content over, want die vrijheid heeft onder meer geleid tot een aantal prachtige publicaties die we in eerste instantie niet voor oog hadden, zoals het population-based onderzoek naar acute myeloïde leukemie (AML) en acute lymfatische leukemie (ALL) in Nederland, die beide zijn gepubliceerd in het tijdschrift *Leukemia*. Onze samenwerking was over het algemeen zeer goed, omdat we meestal op dezelfde golflengte zaten. Er zijn ook enkele momenten geweest waarbij we het tegenovergestelde dachten, maar ondanks de tegengesteldheid kwamen we altijd op een constructieve manier terecht op een middenweg. Ik wil je hartelijk bedanken voor de uitstekende begeleiding, want je had, desondanks je drukke schema wat betreft patiëntenzorg, altijd tijd voor mij. Ik kijk uit naar een voortgaande samenwerking op het gebied van population-based onderzoek naar MDS en AML in Nederland, aangezien mijn proefschrift vraagstellingen voor toekomstig onderzoek heeft voortgebracht.

Graag wil ik **prof. dr. Valery Lemmens, prof. dr. Jan Willem Coebergh** en **prof. dr. Gerwin Huls** bedanken voor de bereidheid om zitting te nemen in de kleine promotiecommissie. Beste **Valery**, ik wil je hartelijk bedanken dat jij—als hoofd Onderzoek bij het Integraal Kankercentrum Nederland (IKNL)—mij hebt aangenomen als postdoctoraal onderzoeker om het population-based onderzoek naar hematologische maligniteiten in Nederland in een breder context verder voort te zetten. Daarnaast ben ik je erg dankbaar dat je mij een deelaanstelling hebt aangeboden bij de afdeling Maatschappelijke Gezondheidszorg van het Erasmus MC, waar jij tevens bijzonder hoogleraar bent. Beste **Jan Willem**, we kennen elkaar inmiddels een aantal jaren via PHAROS. Ik wil je bedanken voor de gesprekken die we tijdens of na de PHAROS bijeenkomsten hadden over population-based kankeronderzoek, met name over de gegevens met betrekking tot comorbiditeit die sinds 1993 worden verzameld in de regionale kankerregistratie van het voormalig Integraal Kankercentrum Zuid (nu IKNL locatie Eindhoven). De interessante gesprekken die wij hebben gevoerd hebben mij doen besluiten om binnenkort gebruik te maken van deze gegevens bij patiënten met hematologische maligniteiten, in het bijzonder met MDS en AML.

Beste **Gerwin**, ten eerste van harte gefeliciteerd met je recente hoogleraarschap; het ga je goed! Ik hoop in de toekomst ons contact te kunnen voortzetten om zo ook verder samen te kunnen werken op het gebied van population-based onderzoek naar MDS en AML.

Verder wil ik **prof. dr. Jan Cornelissen**, **prof. dr. Peter Huijgens** en **prof. dr. Ulrich Germing** bedanken voor deelname aan de verdediging van mijn proefschrift. Beste **Jan**, ik vond het een waar genoegen om met je samen te werken aan de population-based onderzoeken naar acute leukemieën in Nederland. Ik wil je bedanken voor de tips die je me hebt gegeven wat betreft het schrijven van Engelstalige artikelen; je bent erg goed in het schrijven van soortgelijke artikelen als niet-moedertaalspreker van het Engels. Beste **Peter**, wie had ooit gedacht dat onze wegen zouden kruisen bij het IKNL. Ik hoop in de komende tijd heel veel van je te leren over de oncologische gezondheidszorg in Nederland. Je hebt immers niet voor niets recentelijk de prestigieuze 'Prof. dr. P. Muntendamprijs' gekregen van KWF Kankerbestrijding, vanwege je grote inzet voor de oncologische gezondheidszorg, in het bijzonder de hemato-oncologie. Now I will briefly switch to English as I want to thank **prof. dr. Ulrich Germing** for taking place in the opposition for my thesis defense. Dear **Ulrich**, it is truly an honor for me that you are attending my thesis defense as an opponent. I always read with much interest all your papers that has been published with data from the invaluable Düsseldorf MDS registry. I hope that we can join forces in the near future with our registries to further progress the epidemiologic field of MDS in Europe.

Dit onderzoek was niet mogelijk geweest indien de PHAROS registratie niet was verwezenlijkt door de founding father: **prof. dr. Peter Huijgens**. Ik kan me het nog goed herinneren dat **Peter** het erg leuk vond dat er eindelijk een promovendus werd aangesteld bij PHAROS, aangezien er voor mijn aanstelling slechts promovenda aangesteld waren, namelijk **Djamila**, **Silvia**, **Hedwig**, **Esther**, **Simone** en **Noortje**. Zelfs na mijn aanstelling kwam er nog een promovenda bij, namelijk **Stefanie**. Gaarne wil ik alle bestuurs- en werkgroepleden, alsmede de industrie, de ziekenhuizen en de hematologen bedanken voor hun bijdrage aan PHAROS. Daarnaast wil ik graag nog een aantal personen nadrukkelijk bedanken die deel uitmaakte van PHAROS. Beste **Otto**, ik sta echt versteld over je uitmuntende kennis met betrekking tot de kankerregistratie; het is daarom ook niet raar dat je Directeur Registratie bent van IKNL. Ik vind het erg wonderbaarlijk dat je zoveel ICD-O morfologiecodes uit je hoofd kent. Ik wil je bedanken voor je hulp met het tot stand komen van mijn epidemiologische kennisontwikkeling. Ik hoop tijdens mijn aanstelling bij IKNL nog veel meer van je te mogen leren op het gebied van registratie (en onderzoek). Beste **Yvette**, jouw kennis wat betreft statistiek is erg bewonderenswaardig. Ondanks ik geen leek ben op het gebied van statistiek, heb ik tijdens mijn promotietijd ontzettend veel van je geleerd. De bestaande en ontwikkelde kennis ga ik de komende

jaren verder ontplooien. Ik hoop dat ik in de toekomst nog altijd een beroep op je kan doen als ik wil sparren over bepaalde statistische methodologieën. Beste **Ward**, ik wil je bedanken voor je enthousiasme en spontaniteit wat betreft mijn onderzoek, alsmede je bijdrage aan enkele artikelen die beschreven zijn in dit proefschrift. Beste **Hind** en **Liyan**, jullie hebben echt top werk verricht om patiëntengegevens te vergaren voor de PHAROS MDS registry. Mede dankzij jullie inzet zijn er twee hoofdstukken in dit proefschrift tot stand gekomen, die uiteraard gebaseerd zijn op gegevens uit de PHAROS MDS registry.

Het onderzoek dat beschreven is in dit proefschrift is grotendeels gebaseerd op gegevens van de oncologische schatkist van Nederland, namelijk de landelijk dekkende Nederlandse Kankerregistratie (NKR) die sinds 1989 operationeel is. Ik wil alle registratiemedewerkers van de NKR heel erg bedanken voor al het harde werk dat sinds 1989 wordt geleverd om gegevens van alle nieuw gediagnosticeerde kankerpatiënten in Nederland te registeren in de NKR. Met name dankzij jullie inzet is de NKR een schatkist met waardevolle gegevens die de oncologische gezondheidszorg kunnen bevorderen. Daarnaast wil ik in het bijzonder de deelnemende patiënten enorm bedanken voor hun onontbeerlijke bijdrage aan zowel de NKR als PHAROS.

Tevens gaat mijn dank uit naar mijn collegae van de afdeling Hematologie van het Erasmus MC. Ik wil met name alle collegae van de 13e verdieping bedanken, die zich overigens overwegend bezig houden met moleculair onderzoek, voor de interesse in mijn klinisch epidemiologisch onderzoek. Ik vond het altijd erg leuk (en ook uitdagend) om mijn onderzoek aan jullie te presenteren. Voorts wil ik in deze alinea specifiek een aantal mensen bedanken van de afdeling Hematologie van het Erasmus MC, ongeacht op welke verdieping men werkzaam is. Beste **Kirsten**, hartelijk bedankt dat je bereid was om een aantal fraaie morfologieplaatjes van MDS, chronische myelomonocytaire leukemie (CMML) en AML te selecteren voor de kaft en hoofdstukken van mijn proefschrift. Je bent niet voor niets een morfoloog, aangezien je oog voor detail de nodige bijstellingen aan de kaft van mijn proefschrift teweeg hebben gebracht; bedankt daarvoor. Daarnaast wil ik je ook bedanken voor de mogelijkheid die je me bood om geschoold te worden in de morfologie van het bloed en beenmerg bij jou op het lab. Voor de scholing wil ik in het bijzonder **Trudi** bedanken. Beste **Trudi**, je hebt me destijds bij aanvang van mijn promotietraject heel goed geleerd hoe je specifieke cellen in het bloed en beenmerg moet herkennen. Mijn HLO-opleiding heeft me geholpen om dit redelijk snel op te pakken; het was immers weer een tijdje geleden dat ik van het HLO afkwam. Het is onbetwist dat je excellente kennis van de morfologie van het bloed en beenmerg cruciaal is geweest voor mijn ontwikkeling wat betreft MDS, een ziekte waar de morfologische beoordeling van het bloed en beenmerg ten grondslag ligt voor de classificatie van dit ziektebeeld.

Beste **Egied**, hartelijk dank voor al het keurige werk dat je hebt geleverd om dit proefschrift lay-out technisch goed er uit te laten zien. Het is noemenswaardig dat je zelfs tijdens je vakanties in Spanje en Portugal tijd hebt vrijgemaakt om aan mijn proefschrift te knutselen; mijn dank daarvoor is groot. Beste **Inge**, ik vond het erg fijn om met je samen te werken op het population-based onderzoek naar CMML in Nederland. Daarnaast hartelijk bedankt voor je bijdrage aan het artikel dat daaruit is voortgevloeid. Beste **Anita**, hartelijk bedankt voor de plezierige samenwerking omtrent het population-based onderzoek naar ALL in Nederland. Deze samenwerking heeft geresulteerd in een prachtige publicatie in *Leukemia*. Ik voorzie in de nabije toekomst dat we blijven samenwerken op dit specifieke gebied. Daarnaast moeten we niet al te vaak overleggen in een spreekkamer op de sikkelcelpoli op D3, aangezien men dan denkt dat ik mogelijk een patiënt van je ben. Beste **Sarah** en **Eric Braakman**, ik wil jullie beide hartelijk bedanken dat ik naast mijn promotieonderzoek ook de mogelijkheid heb gekregen om onder jullie hoede diverse organisatorische taken uit te voeren voor de afdeling Hematologie. Deze werkzaamheden hebben mijn kennis en kunde (lees CV) verreikt voor toekomstige werkzaamheden. Beste **Ed**, jammer dat je niet meer in Utrecht werkt, want het is echt een geweldige stad.

Wat ben ik blij dat **Boyke Djorai** en **Jurjen Versluis** tijdens mijn verdediging aan mijn zijde willen staan als paranimfen. **Boyke**, jij bent mijn oudste (en wijste) neef, maar ik zie je meer als mijn grote broer waar ik altijd naar op kijk. Jij hebt mij geleerd dat je klein moet beginnen om groot te eindigen. Jij bent daar een goed schoolvoorbeeld van in vele facetten, waaronder je pad met betrekking tot je studie en je daaropvolgende loopbaan. Beste **Jurjen**, het was eigenlijk al bij onze eerste ontmoeting duidelijk dat we het goed met elkaar zouden kunnen vinden. Jij was overigens toentertijd de enige promovendus op de 13e die wist waar mijn onderzoek overging, zowel inhoudelijk als methodologisch. Ondanks je een aantal jaren bezig bent met de opleiding interne geneeskunde, hebben we van tijd tot tijd gelukkig nog erg goed contact. Ik hoop dat we nog vele jaren goed bevriend zullen blijven en dat we vaker contact zullen hebben.

Lieve **mama**, het gaat soms je pet te boven wat betreft de inhoudelijke kant van mijn promotieonderzoek. Desalniettemin heb je me ten alle tijden uitstekend ondersteund met alles wat ik graag wilde doen. Ik ben werkelijk niks te kort gekomen en daar waardeer ik je enorm voor. Vanwege je onvoorwaardelijke liefde en steun ben ik nu de persoon geworden die vandaag de dag hier staat. Zonder je steun, toen en nu, was ik waarschijnlijk nooit zo ver gekomen als nu. Het is uiterst tevredenstellend om een moeder te hebben die zo ontzettend trots is. Nogmaals bedankt voor alles!

Tot slot volgt de laatste alinea die speciaal is toegewijd aan mijn lieve **Damian** en **Priscilla**. Lieve **Damian**, jij bent het allerbeste wat mij is overkomen. Je bent inmiddels bijna 5 jaar en je begrijpt steeds beter dat ik als 'onderzoeker' ook kan werken 'in een ziekenhuis in Rotterdam' om 'mensen beter te maken'. Ondanks het feit dat je nog niet zo goed begrijpt dat ik geen normale 'dokter' ben, zeg je vaak thuis en op school dat je ook een 'dokter' wilt worden net als papa. Ik ontken het niet, maar het lijkt me erg leuk als we later samen onderzoek kunnen doen op het gebied van kankerepidemiologie. Lieve **Priscilla**, ik wil je bedanken voor je liefde (die deels door mijn maag ging), geduld, steun, afleiding en begrip die ik zonder meer nodig had om mijn enigszins chaotische leven wat betreft mijn promotieonderzoek door te komen. Daarnaast wil ik je bedanken dat je er altijd voor me bent geweest. Hoewel het harde werk soms ten koste ging van onze vrije tijd, wil ik je tevens bedanken voor de talloze prachtige momenten die we samen hadden. Naast dat je een zorgzame moeder bent voor onze prachtige zoon en een geweldige vrouw bent voor mij, ben je momenteel ook nog een vierdejaars student Financial Services Management. Ik wens je heel veel succes toe met het afronden van je studie; jij hebt het namelijk ook erg druk met je studie, Damian en mij. In een zekere zin hebben we elkaar de afgelopen 4 jaar bijgestaan en ondersteund om onze doelen te verwezenlijken op het gebied van studie en werk. Het is duidelijk dat we complementair zijn aan elkaar. Binnenkort komen er wat minder chaotische tijden aan, waarbij we nog meer van onze mooie gezin kunnen genieten; ik kijk er zeer naar uit!

Ik heb gezegd (of mag/kan dat alleen bij een oratie?).

Avinash Dinmohamed
Mei 2016

List of publications

PUBLICATIONS IN THIS THESIS

1. **Dinmohamed AG**, Visser O, Posthuma EF, Huijgens PC, Sonneveld P, van de Loosdrecht AA, Jongen-Lavrencic M. 2016. Diagnosis and treatment of myelodysplastic syndromes and chronic myelomonocytic leukemia in daily practice: results from the Dutch population-based PHAROS MDS registry. 2016. Submitted in modified form.

2. **Dinmohamed AG**, Visser O, van Norden Y, Blijlevens NM, Cornelissen JJ, Huls GA, Huijgens PC, Sonneveld P, van de Loosdrecht AA, Ossenkoppele GJ, Löwenberg B, Jongen-Lavrencic M. Treatment, trial participation and survival in adult acute myeloid leukemia: a population-based study in the Netherlands, 1989-2012. *Leukemia*. 2016 Jan;30(1):24-31.

3. **Dinmohamed AG**, van Norden Y, Visser O, Posthuma EF, Huijgens PC, Sonneveld P, van de Loosdrecht AA, Jongen-Lavrencic M. Effectiveness of azacitidine for the treatment of higher-risk myelodysplastic syndromes in daily practice: results from the Dutch population-based PHAROS MDS registry. *Leukemia*. 2015 Dec;29(12):2449-51.

4. **Dinmohamed AG**, Brink M, Visser O, Sonneveld P, van de Loosdrecht AA, Jongen-Lavrencic M, de Greef GE. Trends in incidence, primary treatment and survival in chronic myelomonocytic leukaemia: a population-based study of 1359 patients diagnosed in the Netherlands from 1989 to 2012. *Br J Haematol*. 2015 Nov;171(3):436-9.

5. **Dinmohamed AG**, van Norden Y, Visser O, Posthuma EF, Huijgens PC, Sonneveld P, van de Loosdrecht AA, Jongen-Lavrencic M. The use of medical claims to assess incidence, diagnostic procedures and initial treatment of myelodysplastic syndromes and chronic myelomonocytic leukemia in the Netherlands. *Leuk Res*. 2015 Feb;39(2):177-82.

6. **Dinmohamed AG**, Visser O, van Norden Y, Huijgens PC, Sonneveld P, van de Loosdrecht AA, Jongen-Lavrencic M. Trends in incidence, initial treatment and survival of myelodysplastic syndromes: a population-based study of 5144 patients diagnosed in the Netherlands from 2001 to 2010. *Eur J Cancer*. 2014 Mar;50(5):1004-12.

OTHER PUBLICATIONS

1. **Dinmohamed AG**, Brink M, Visser O, Jongen-Lavrencic M. Population-based analyses among 184 patients diagnosed with large granular lymphocyte leukemia in the Netherlands between 2001 and 2013. *Leukemia*. 2016. Accepted for publication.

2. **Dinmohamed AG**, Szabó A, van der Mark M, Visser O, Sonneveld P, Cornelissen JJ, Jongen-Lavrencic M, Rijneveld AW. Improved survival in adult patients with acute lymphoblastic leukemia in the Netherlands: a population-based study on treatment, trial participation and survival. *Leukemia*. 2016 Feb;30(2):310-7.

3. **Dinmohamed AG**, Visser O, van Norden Y, Huijgens PC, Sonneveld P, van de Loosdrecht AA, Jongen-Lavrencic M. Het myelodysplastisch syndroom in Nederland: een population-based onderzoek naar incidentie, primaire behandeling en overleving in de periode 2001-2010. *Ned Tijdschr Hematol*. 2015 Mar; 12:47-57.

4. Erkens CG, **Dinmohamed AG**, Kamphorst M, Toumanian S, van Nispen-Dobrescu R, Alink M, Oudshoorn N, Mensen M, van den Hof S, Borgdorff M, Verver S. Added value of interferon-gamma release assays in screening for tuberculous infection in the Netherlands. *Int J Tuberc Lung Dis*. 2014 Apr;18(4):413-20.

5. Annoura T, van Schaijk BC, Ploemen IH, Sajid M, Lin JW, Vos MW, **Dinmohamed AG**, Inaoka DK, Rijpma SR, van Gemert GJ, Chevalley-Maurel S, Kiełbasa SM, Scheltinga F, Franke-Fayard B, Klop O, Hermsen CC, Kita K, Gego A, Franetich JF, Mazier D, Hoffman SL, Janse CJ, Sauerwein RW, Khan SM. Two Plasmodium 6-Cys family-related proteins have distinct and critical roles in liver-stage development. *FASEB J*. 2014 May;28(5):2158-70.

PhD portfolio

SUMMARY OF PHD TRAINING AND TEACHING ACTIVITIES

Name PhD candidate:	A.G. Dinmohamed
PhD period:	October 2011 - October 2015
Erasmus MC department:	Hematology
Promotors:	Prof. dr. P. Sonneveld
	Prof. dr. A.A. van de Loosdrecht
Research school:	Molecular Medicine
Supervisor:	Dr. M. Jongen-Lavrencic

Activities	Year	ECTS
1. PhD training		
General academic/research skills		
Introduction to clinical research (NIHES)	2011	0.9
Biostatistics for clinicians (NIHES)	2011	1.0
Regression analysis for clinicians (NIHES)	2011	1.9
Survival analysis for clinicians (NIHES)	2011	1.9
Basiscursus regelgeving en organisatie van klinisch onderzoek	2012	1.0
Course for the Quantitative Researcher (NIHES)	2012	1.4
Biomedical writing course for MSc students and PhD students (MolMed)	2013	2.0
Repeated Measurements in Clinical Studies (NIHES)	2014	1.4
The Survival Analysis Course (MolMed)	2014	0.5
Seminars and workshops		
Symposium Hematomorfologie Rotterdam (2x)	2012-2014	0.5
Molecular aspects of hematologic malignancies	2014	0.6
Cursus Morfologie Bloed	2012	0.3
Regionale Nascholing Hematologie Rotterdam (3x)	2012-2015	0.9
Clinical updates in Hematology on AML and MDS (Budapest, Hungary)	2013	0.6
Writing Successful Grant Proposals	2014	0.5
Erasmus Hematology Lectures	2011-2015	3
National and international conferences		
Annual congress of the American Society for Hematology (1x)	2014	1
Annual congress of the European Hematology Association (4x)	2012-2015	4
Annual Dutch Hematology Congress (3x)	2013-2015	1.5
Molecular Medicine Day (2x)	2013-2014	0.6
Oral presentations		
Dutch Hematology Congress (3x)	2013-2015	3
Annual congress of the European Hematology Association (1x)	2013	1
Work discussions at Department of Hematology, Erasmus MC (6x)	2011-2015	5
Journal club at Department of Hematology, Erasmus MC (2x)	2011-2015	1
AIO/post-doc meeting at Department of Hematology, Erasmus MC (3x)	2011-2015	1.5
PHAROS work discussions (4x)	2011-2014	2
MDS Celgene Sounding Board Meeting (1x)	2015	0.5
Poster presentations		
Annual congress of the American Society for Hematology (1x)	2014	1
Annual congress of the European Hematology Association (2x)	2014-2015	2
Molecular Medicine Day	2013	1
Scientific meetings		
AIO/post-doc meetings at the Department of Hematology, Erasmus MC	2011-2015	1.5
Weekly work discussions at the Department of Hematology, Erasmus MC	2011-2015	5
Journal club at the Department of Hematology, Erasmus MC	2011-2015	2
2. Teaching activities		
Supervising data managers		
PHAROS MDS data managers (2x)	2012-2014	4
Supervising practical training and excursions		
Organization and supervision invited PhD lunch sessions	2013-2014	0.3
Medical student blood and bone marrow morphology traininig	2014	0.4
Total		**56.7**

About the author

Avinash Dinmohamed was born on August 26th, 1986 in the Hague, the Netherlands. In 2004, he completed his pre-university education (HAVO) at the TMO College in the Hague. He then attended the University of Applied Sciences in Leiden where he graduated in 2008 with a Bachelor's degree in Biology and Medical Laboratory Sciences with a specialization in Medical Microbiology. Subsequently, in 2010, he graduated with a Master's degree in Biomedical Sciences with specializations in (i) Infectious Diseases and (ii) International Public Health from the VU University in Amsterdam. He conducted his first and second master's theses at the Department of Parasitology of the Leiden University Medical Center (LUMC) on the subject of vaccine development in malaria under the supervision of B.M.D Franke-Fayard, PhD and S.M. Khan, PhD, respectively. His final master's thesis dealt with the evaluation of a specific interferon-gamma release assay (QuantiFERON-TB® Gold In-Tube test) utilized for the diagnosis of latent tuberculosis infection at the Municipal Health Service (GGD) in the Hague under the supervision of E.M. Huisman, MD, MPH and S. Verver, PhD. After completing his master's degree, he worked as a scientific researcher at the KNCV Tuberculosis Foundation on a subject that was in line with his final master's thesis, namely on the evaluation of the implementation of the interferon-gamma release assay for the diagnosis of latent tuberculosis infection in the Netherlands. In October 2011, he started with his PhD training program at the Department of Hematology of the Erasmus MC Cancer Institute in Rotterdam as described in this thesis, under the supervision of Prof. P. Sonneveld, MD, PhD, Prof. A.A. van de Loosdrecht, MD, PhD and Mojca Jongen-Lavrencic, MD, PhD. As of October 2015, he works as a postdoctoral researcher at the Netherlands Comprehensive Cancer Organisation (IKNL) to continue population-based research on hematological malignancies, in particular myelodysplastic syndromes and acute myeloid leukemia. In addition, he is an affiliated researcher at the Department of Hematology of the Erasmus MC Cancer Institute in Rotterdam as well as at the Department of Public Health of the Erasmus University Medical Center in Rotterdam.