Treatment patterns in older patients with myelodysplastic syndromes

HemoBase Population Registry Consortium; Rozema, Johanne; Graafsma, Jetske; Hoogendoorn, Mels; Kibbelaar, Robby; Veeger, Nic; van Roon, Eric

Published in:
Journal of Geriatric Oncology

DOI:
10.1016/j.jgo.2022.101418

Publication date:
2023

Journal of Geriatric Oncology 14 (2023) 101418

Contents lists available at ScienceDirect

Journal of Geriatric Oncology

journal homepage: www.elsevier.com/locate/jgo

Research Paper

Treatment patterns in older patients with myelodysplastic syndromes: A population-based analysis reflecting the real world

Johanne Rozema [a,b,*], Jetske Graafsma [a], Mels Hoogendoorn [c], Robby Kibbelaar [d], Nic Veeger [e,f], Eric van Roon [a,b], On behalf of the HemoBase Population Registry Consortium [1]

[a] Unit of Pharmacotherapy, Epidemiology and Economics, Department of Pharmacy, University of Groningen, Antonius Deusinglaan 1, Groningen, the Netherlands
[b] Department of Clinical Pharmacy & Pharmacology, Medical Centre Leeuwarden, Henri Dunantweg 2, Leeuwarden, the Netherlands
[c] Department of Internal Medicine, Medical Centre Leeuwarden, Henri Dunantweg 2, Leeuwarden, the Netherlands
[d] Pathology Friesland, Jelsumerstraat 6a, Leeuwarden, the Netherlands
[e] MCL Academy, Medical Centre Leeuwarden, Henri Dunantweg 2, Leeuwarden, the Netherlands
[f] Department of Epidemiology, University of Groningen, University Medical Centre Groningen, Hanzeplein 1, Groningen, the Netherlands

ARTICLE INFO

Keywords:
Treatment duration
Drug survival
Myelodysplastic syndromes
Population-based

ABSTRACT

Introduction: Treatment for myelodysplastic syndromes (MDS) is complex, options are limited, and insight into consecutive treatments is lacking. We performed this study to assess the outcomes in a real-world cohort of patients with MDS.
Materials and Methods: An observational population-based study was performed using the HemoBase registry. Treatment patterns and overall survival (OS) were analyzed with Kaplan-Meier analyses.
Results: In 144 of 280 (51.4%) patients with MDS >50 years, first-line treatment was initiated. The median age was 75.1 years (range: 52.6–92.0); the majority were male (72.2%). Hypomethylating agents (HMA), intensive chemotherapy, lenalidomide, and erythropoiesis-stimulating agents (ESA) were given as first-line treatment to 31.1% ($n = 45$), 12.5% ($n = 18$), 2.8% (n = 4), and 53.5% ($n = 77$) of the population, respectively. The median treatment duration was 5.8 months (95% Confidence Interval [CI]: 1.1–10.4) for HMA, 1.7 months (95%CI: 0.9–2.6) for intensive chemotherapy, 10.8 months (95%CI: 4.7–17.0) for lenalidomide, and 14.8 months (95%CI: 11.4–18.1) for ESA. Consecutive treatments were given to 27.2% of patients. The main reasons for first-line treatment discontinuation were treatment failure (45.8%), toxicity (6.9%), or death (20.1%). Median OS after termination of the initial, second, and third treatment was 5.8 months (95%CI: 3.2–8.5), 9.3 months (95%CI: 0.0–19.6), and 1.0 months (95%CI: 0.0–5.1), respectively.
Discussion: This study shows the treatment outcomes in a real-world population of older patients with MDS. Treatment duration and median OS after treatment discontinuation were relatively limited. There is still an urgent need for new treatment options, strategies to further optimize duration of existing treatments, and communication of realistic treatment goals and expectations, especially for older, higher-risk patients with MDS with a poor prognosis.

1. Introduction

Myelodysplastic syndromes (MDS) are a group of hematological malignancies characterized by inefficient hematopoiesis and are predominantly diagnosed in older patients [1,2]. They are heterogeneous diseases with a wide variety of clinical courses [3–5]. A watch and wait strategy can be appropriate, or patients with MDS can receive active treatment. Despite the evolving field of cancer treatment, monotherapy is still the basis of treatment in patients with MDS [6,7]. Treatment options vary for different MDS subtypes and may consist of erythropoiesis stimulating agents (ESA) to improve anemia, intensive chemotherapy, and chemo-immunomodulating therapy such as hypomethylating agents (HMA) and lenalidomide to delay disease progression [1,5,8]. Unfortunately, the response to these agents, the

* Corresponding author at: University of Groningen / Medical Center Leeuwarden, Department of Clinical Pharmacy & Pharmacology, P.O. Box 888, 8901 BR Leeuwarden, the Netherlands.
E-mail addresses: hanne.rozema@rug.nl, hanne.rozema@mcl.nl (J. Rozema).
[1] A list of the HemoBase Population Registry Consortium appears in the acknowledgements.

https://doi.org/10.1016/j.jgo.2022.101418
Received 2 March 2022; Received in revised form 27 June 2022; Accepted 8 December 2022
Available online 17 January 2023

toxicity and the observed prolonged survival shown in clinical trials may not reflect daily clinical practice, as patients with MDS outside clinical trials tend to be older and have more comorbidities than patients in clinical trials [4,8–14]. Treatment options for patients with MDS are limited, and selecting the optimal strategy to prevent treatment failure is challenging [8,12,15]. Failure of initial treatment yields several problems. Firstly, only few therapeutic alternatives are available after failure of initial treatment [4,8,15]. Secondly, the potential alternatives often have similar toxicity profiles and may therefore not always be suitable for vulnerable older patients [8,16]. Since the treatment options are limited, optimizing first-line treatment is essential.

The Netherlands Cancer Registry (NCR) recently published a report regarding first-line treatment in patients with MDS diagnosed from 2014 to 2018 [17]. This report observed that a large proportion of patients received no treatment, ranging from 20% in patients with higher-risk MDS to 50% in patients with lower-risk MDS [17]. Data about consecutive treatments were not available in this nationwide registry, and other studies analyzing treatment patterns and outcomes in patients with MDS are lacking [17]. Therefore, we conducted this research to provide insights into initial and consecutive treatments in patients with MDS; assessed treatment duration, consecutive treatment patterns, reasons for treatment discontinuation or switching; and presented overall survival (OS) after treatment discontinuation in a real-world cohort of patients with MDS.

2. Methods

A retrospective population-based study was performed using the HemoBase population registry [18,19]. HemoBase is a multidisciplinary electronic patient file that contains clinical information about patients diagnosed with a hematological malignancy since 2005 in Friesland, a province in the Netherlands with approximately 650,000 inhabitants [18]. The Medical Ethics Committee in Leeuwarden confirmed the conduct of this retrospective study without the need for ethical review, and the institutional boards approved its execution without the need for consent in accordance with the Declaration of Helsinki (2013 revision) and Dutch regulations.

In this study, HMA (azacitidine and decitabine), intensive chemotherapy, lenalidomide, and ESA (+/− granulocyte-colony stimulating factor) were considered indicated treatments for MDS. Azacitidine is registered by the European Medicines Agency (EMA) for patients with an International Prognostic Scoring System (IPSS) score of intermediate-2 or high-risk MDS who are ineligible for transplantation therapy. Decitabine, although not officially EMA-registered for MDS, is administered to patients with higher-risk MDS [16,20,21]. Intensive chemotherapy (e.g. cytarabine, daunorubicine) based on treatment protocols for acute myeloid leukemia (AML) is a treatment option for patients with higher-risk MDS, such as MDS with excess blasts (MDS-EB) [20–22]. Lenalidomide is registered as monotherapy for transfusion-dependent patients with IPSS low and intermediate-1 risk MDS with an isolated 5q deletion after failure of other treatment options or when other treatments are insufficient or not adequate [6,16]. ESA are registered for treatment of symptomatic anemia (Hb $\leq$10 g/dL or $\leq$ 6.2 mmol/L) in patients with IPSS low or intermediate-1 risk MDS [6,16]. Luspatercept as a treatment option was not included in this study, as it was not yet registered at the time of patient follow-up [16].

All persons newly diagnosed with MDS in the Frisian hospitals between January 1, 2005 and December 31, 2017 and with age at diagnosis >50 years were identified and included in this study. Patients were observed from date of diagnosis to date of death or end of follow-up (June 2019). Patients who received one or more of the indicated treatments were considered as being treated. Patients who did not receive treatment were considered being on a watch and wait strategy and received supportive care. Clinical information about patient characteristics, such as age, comorbidities (Charlson Comorbidity Index [CCI]), MDS subtype, and treatment characteristics, was collected from electronic health records.

Revised IPSS (IPSS-R) categories very low, low, and intermediate were defined as lower-risk MDS and IPSS-R categories high and very high as higher-risk MDS [23]. Patients with an unknown IPSS-R category due to unsuccessful bone marrow biopsies or missing cytogenetic data were presented as a separate group. Treatment duration was defined as the time between start and termination of treatment [24]. Time to first-line treatment was defined as the time between diagnosis and the start of initial treatment. Reasons for treatment discontinuation were based on the information in hospital records and on the physician's judgment in cases of ambiguity. These reasons were categorized as treatment failure, toxicity, contraindication, deceased, or other. Treatment failure included progressive disease and insufficient or no response, as defined according to the response criteria of the International Working Group [25]. The category other included preparation for transplantation, patient request, or unknown. Treatment duration and OS were depicted using the Kaplan-Meier method [24,26,27]. In addition, median survival times and 95% confidence intervals (CI) were estimated. Patients with missing information on start and/or stop dates were omitted from the Kaplan-Meier analysis. Patients were censored in case treatment was still ongoing by the end of follow-up. Log rank analyses were used to determine differences in median OS between groups after treatment discontinuation. Initial and consecutive treatments were analyzed separately. To study consecutive treatment patterns, a descriptive flow chart was made for all patients receiving treatment. In this chart, patients were retrospectively considered “at risk” for a consecutive treatment if they had discontinued their first treatment, except for patients deceased within a day of treatment discontinuation, so all potential cases were included. Statistical analyses were performed using IBM SPSS version 24.

2.1. Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

3. Results

A total of 280 patients with MDS with age at diagnosis >50 years were identified, 144 (51.4%) of whom received first-line treatment (Table 1, Fig. 1). The median age of the population was 75.1 years (range: 52.6–92.0), the majority was male (72.2%), and approximately half (56.9%) of the population was considered lower-risk MDS. Twenty-seven patients eventually progressed to AML.

Fig. 1 presents which treatments were given during follow-up. HMA, intensive chemotherapy, lenalidomide, and ESA were given to 38.2% (n = 55), 20.8% (n = 30), 5.6% (n = 8), and 54.9% (n = 79) of the population during any treatment line, respectively, and to 31.3% (n = 45), 12.5% (n = 18), 2.8% (n = 4), and 53.5% (n = 77) of the population as first-line treatment (Table 1). Of those treated with HMA and intensive chemotherapy, 26 (47.3%) and 14 (46.7%) were patients with lower-risk MDS, respectively. Eighteen patients (12.5%) received an allogeneic stem cell transplant (SCT), eight of whom had intensive chemotherapy as first-line treatment. A second treatment was given to 27.2% (n = 28) of the population at risk; 30.8% (n = 8) of these patients at risk received a third treatment, and 42.9% (n = 3) received a fourth treatment (Fig. 1). After initial treatment, patients predominantly switched to intensive chemotherapy (46.4%, n = 13; 7 of these patients ultimately received SCT) or HMA (35.7%, n = 10, Fig. 1). The median treatment duration of initial treatment was 5.8 months (95% CI: 1.1–10.4) for HMA, 1.7 months (95% CI: 0.9–2.6) for intensive chemotherapy, 10.8 months (95%CI: 4.7–17.0) for lenalidomide, and 14.8 months (95% CI: 11.4–18.1) for ESA (Fig. 2). The median time to start of initial treatment was 4.1 months (95% CI: 2.3–9.7) for HMA, 2.4 months (95% CI: 1.5–14.3) for intensive chemotherapy, 18.9 months (95% CI: 0.2–47.9) for lenalidomide, and 4.3 months (95% CI: 2.7–6.3) for ESA.

Table 1
Baseline patient characteristics divided by treatment type.

	HMA	Intensive chemotherapy	Lenalidomide	ESA	Total[a]
	N (%)	N (%)	N (%)	N (%)	N (%)
Total	55 (100)	30 (100)	8 (100)	79 (100)	144 (100)
First line treatment	45 (81.8)	18 (60.0)	4 (50.0)	77 (97.5)	144 (100)
Age					
51–60	5 (9.1)	11 (36.7)	0 (0)	4 (5.1)	15 (10.4)
61–70	20 (36.4)	9 (30.0)	1 (12.5)	13 (16.5)	33 (22.9)
71–80	22 (40.0)	8 (26.7)	6 (75.0)	39 (49.4)	64 (44.4)
>80	8 (14.5)	2 (6.7)	1 (12.5)	23 (29.1)	32 (22.2)
Median (range)	72.4 (54.2–85.4)	63.2 (52.6–86.3)	76.8 (66.0–84.3)	77.6 (52.6–92.0)	75.1 (52.6–92.0)
Male sex	41 (74.5)	23 (76.7)	5 (62.5)	55 (69.6)	104 (72.2)
MDS Subtype					
SLD	7 (12.7)	3 (10.0)	1 (12.5)	11 (13.9)	17 (11.8)
MLD	9 (16.4)	2 (6.7)	1 (12.5)	15 (19.0)	20 (13.9)
RS-SLD	1 (1.8)	1 (3.3)	1 (12.5)	24 (30.4)	25 (17.4)
RS-MLD	3 (5.5)	1 (3.3)	0 (0)	13 (16.5)	17 (11.8)
Del 5q	0 (0)	1 (3.3)	4 (50.0)	1 (1.3)	5 (3.5)
EB-1	17 (30.9)	7 (23.3)	1 (12.5)	7 (8.9)	27 (18.8)
EB-2	14 (25.5)	9 (30.0)	0 (0)	3 (3.8)	20 (13.9)
U	1 (1.8)	2 (6.7)	0 (0)	1 (1.3)	3 (2.1)
n.o.s.	3 (5.5)	4 (13.3)	0 (0)	4 (5.1)	10 (6.9)
IPSS-R category					
Low risk	26 (47.3)	14 (46.7)	7 (87.5)	50 (63.3)	82 (56.9)
High risk	22 (40.0)	9 (30.0)	1 (12.5)	8 (10.1)	29 (20.1)
Unknown	7 (12.7)	7 (23.3)	0 (0)	21 (26.6)	33 (22.9)
CCI score					
0	20 (36.4)	14 (46.7)	3 (37.5)	24 (30.4)	49 (34.0)
1	10 (18.2)	8 (26.7)	3 (37.5)	17 (21.5)	29 (20.1)
≥2	25 (45.5)	8 (26.7)	2 (25.0)	38 (48.1)	66 (45.8)

Abbreviations: ESA: Erythropoiesis stimulating agent, HMA: Hypomethylating agent, MDS: myelodysplastic syndromes, SLD: Single line dysplasia, MLD: Multi line dysplasia, RS: Ring sideroblasts, Del 5q: Deletion of 5q chromosome, EB: Excess blasts, U: Unclassifiable, n.o.s.: not otherwise specified, IPSS-R: Revised international prognostic scoring system, CCI: Charlson comorbidity index. [a] Patients can receive ≥1 treatment, hence totals may differ from the sum of patients per treatment type.

The most important reasons for treatment discontinuation were treatment failure (45.8%), toxicity (6.9%), or death (20.1%, Table 2). There were no significant differences in median age ($p = 0.76$), IPSS-R score ($p = 0.06$), or CCI score ($p = 0.53$) between patients who discontinued due to treatment failure compared to patients who discontinued for other reasons. The median OS after termination of initial treatment was 5.8 months (95% CI: 3.2–8.5, $n = 133$). The median OS after termination of the second and third treatment was 9.3 months (95% CI: 0.0–19.6, $n = 23$) and 1.0 month (95% CI: 0.0–5.1, $n = 6$), respectively. There were no statistically significant differences in median OS for the different treatment types given in the respective treatment lines: $p = 0.65$ for initial treatment, $p = 0.75$ for second treatment, and $p = 0.84$ for third treatment.

We performed additional Kaplan-Meier analyses to compare the median OS of patients who received active treatment and patients who did not. The median OS was better for patients who received active treatment (28.6 months (95% CI: 19.6–37.6)) compared to patients who received supportive care (19.1 months (95% CI: 12.1–26.0)), though not statistically significant ($p = 0.12$). Similarly, we have looked into the median OS after termination of HMA or intensive chemotherapy. For patients who received HMA only, their median OS was 7.0 months (95% CI: 2.7–11.3, $n = 32$), compared to a median OS of 19.0 months (95% CI: 0.0–44.3, $n = 10$) for patients who received active treatment after termination of HMA. However, this difference was not statistically significant ($p = 0.10$). For patients who received intensive chemotherapy only, their median OS was 0.4 months (95% CI: 0.0–1.5, $n = 12$), compared to a median OS of 28.0 months (95% CI: 0.0–63.8, $n = 4$) for patients who received active treatment after termination of HMA ($p = 0.049$).

4. Discussion

In this population-based study comprising a complete and unselected 13-year cohort of patients with MDS aged >50 years, about half of the population of patients with MDS received first-line treatment. A consecutive treatment was given to a quarter of the population at risk. Treatment duration in patients with MDS was limited, and once initial treatment was abrogated, median OS was half a year. Treatment failure was the most important reason for treatment discontinuation.

This study provides insights about the outcomes regarding treatment duration and consecutive treatments offered to patients with MDS in a population-based setting. A quarter of the patients given an initial treatment received a consecutive therapy mainly consisting of intensive chemotherapy or HMA. Interestingly, in some cases, patients received the same treatment type twice. Only two studies published describe consecutive treatments in patients with MDS [28,29]. Park and colleagues focused on the outcomes of patients with lower-risk MDS-RS after ESA failure [29]. Overall, 40% received a consecutive treatment, which was higher than the 29% of patients with ESA who received a consecutive treatment in our study [29]. Tsutsué and colleagues performed a population-based study in Japan amongst patients with lower- and higher-risk MDS and showed that 48% received a consecutive treatment, but blood transfusions, supplied in half of the cases, were also regarded as a treatment modality [28]. The consecutive treatment patterns they described were in line with the results from this study [28]. Population-based studies have shown that 10–40% of patients with MDS receive initial treatment [17,30–33]. This percentage is higher in our study, which may be explained by differences in defining ESA as supportive care or as treatment, as ESA neither modifies the progression of

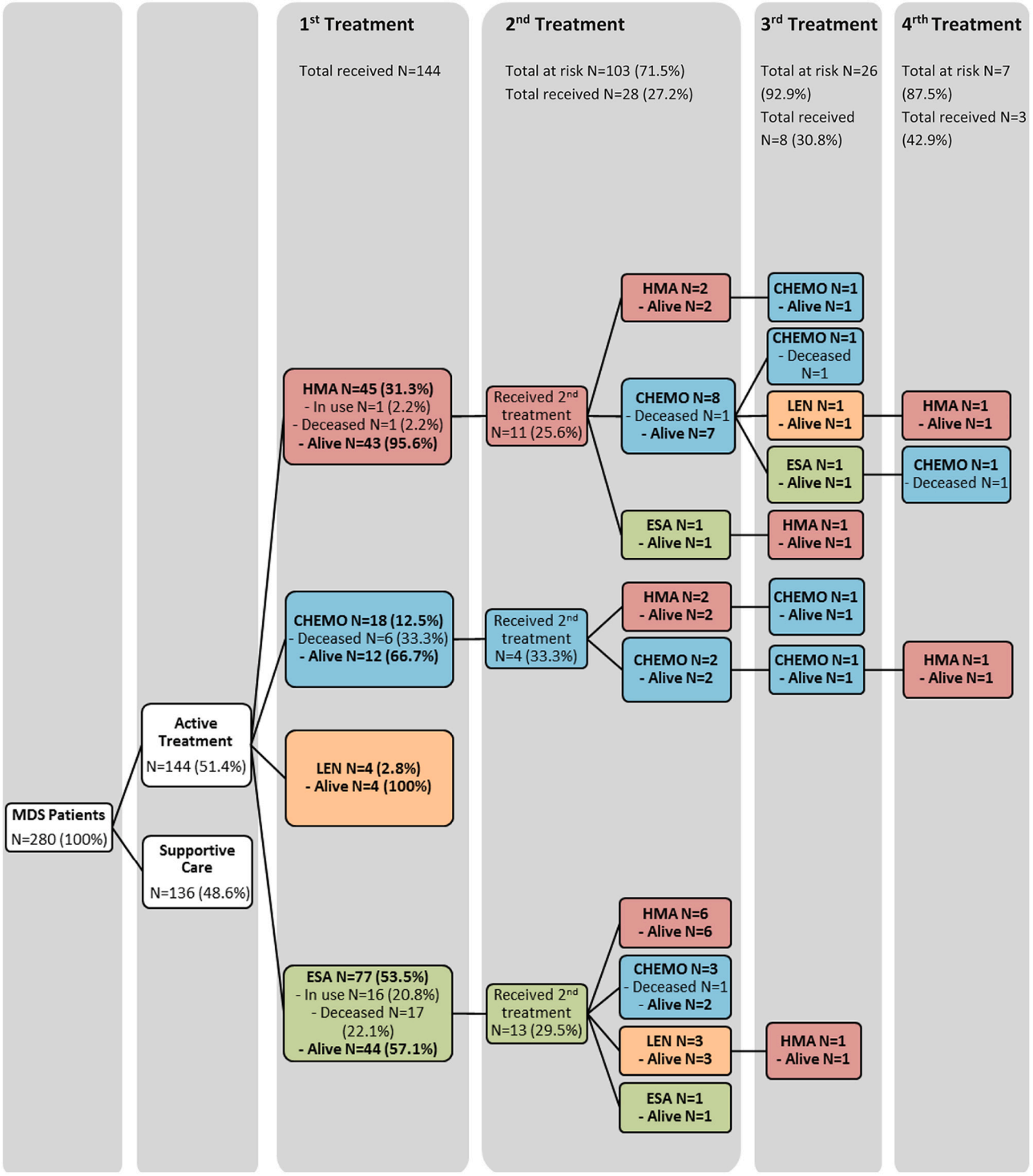

Fig. 1. Flow chart of initial treatment and switching patterns of MDS patients (retrospectively).
Abbreviations: HMA: Hypomethylating agents, CHEMO: Intensive Chemotherapy, LEN: Lenalidomide, ESA: Erythropoiesis stimulating agents.

MDS nor cures the disease [34]. If ESA was classified as supportive care in our study, 30% of patients with MDS would have still received treatment, which aligns with other studies [30–33]. Additionally, only few patients received a transplant, which is in line with other population-based studies [31,32]. During the previous decades in the Netherlands, transplantations amongst patients >65 years were uncommon due to the high treatment-related mortality. Moreover, our study comprises all patients >50 years diagnosed with MDS, including many patients with lower-risk MDS with a relatively good prognosis. These patients are not eligible nor in need of transplantation.

Treatment for MDS is complex and varies across risk groups [3,34]. A watch and wait strategy may be appropriate for some patients, while others require active treatment. There are (inter)national guidelines for initial therapeutic options in MDS, but after failure of initial treatment, further recommendations are less clear [21,22,34–36]. This might explain why our flow chart shows several treatment routes within the study population and within the treatment types, as was also observed in the other population-based study [28].

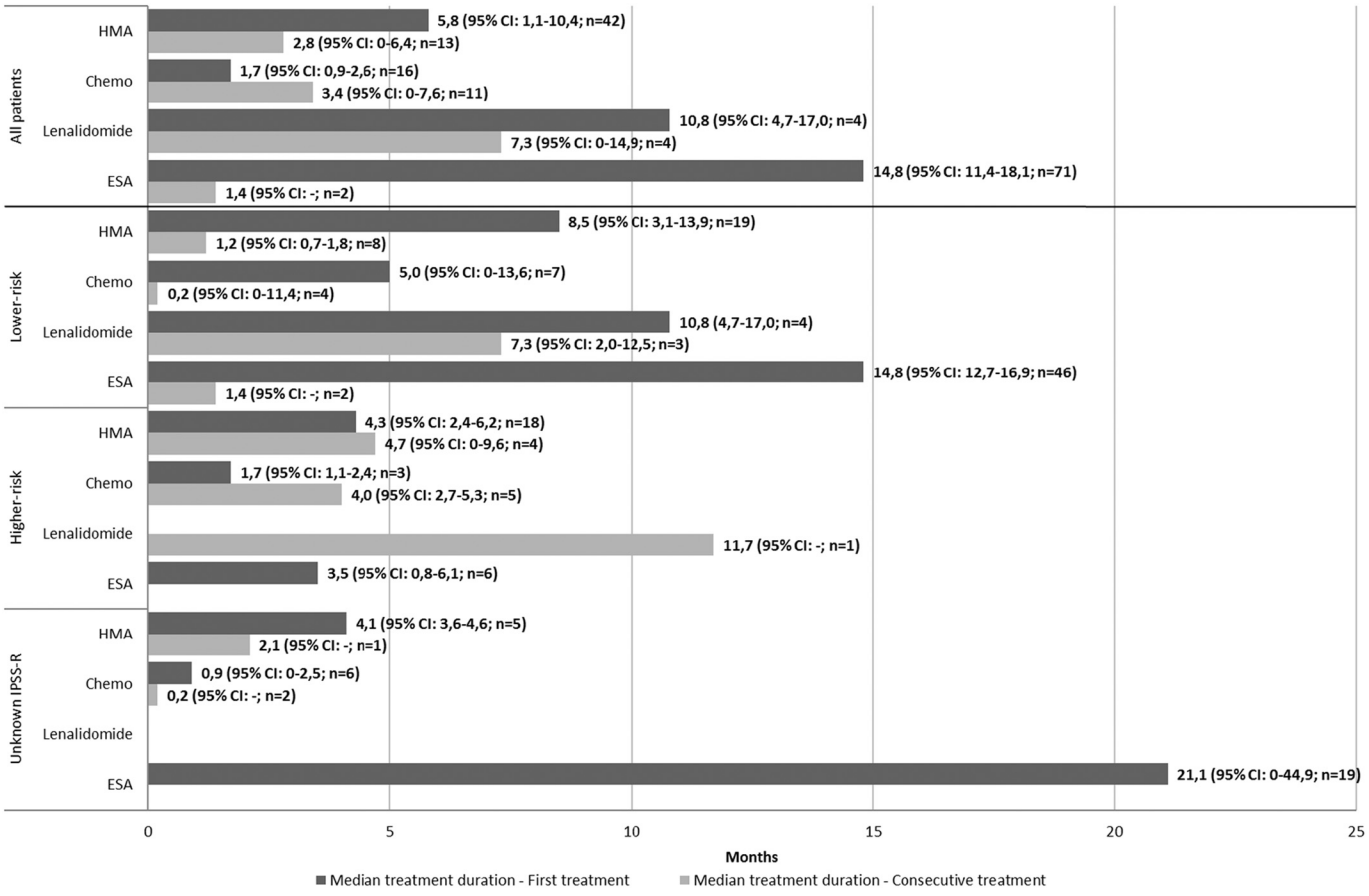

Fig. 2. Median treatment duration of initial and consecutive treatments.
Abbreviations: CI: Confidence interval, HMA: Hypomethylating agents, ESA: Erythropoiesis stimulating agents. The median time to start of initial treatment was 4.1 months (95% CI: 2.3–9.7) for HMA, 2.4 months (95% CI: 1.5–14.3) for intensive chemotherapy, 18.9 months (95% CI: 0.2–47.9) for lenalidomide, and 4.3 months (95% CI: 2.7–6.3) for ESA.

Our study demonstrates that the median duration of different types of treatments for MDS is limited to several months in daily clinical practice. Because of the paucity of treatment options for older patients with MDS, it is vital to optimize and utilize the initial treatment as long as possible. Patients with lower-risk MDS had longer treatment durations than patients with higher-risk MDS. Treatment duration was shortest for patients with intensive chemotherapy, which might be explained by two reasons. Firstly, 31% of patients who received intensive chemotherapy were patients with higher-risk MDS who generally have a poor prognosis. Secondly, intensive chemotherapy may be indicated for a short period of time according to pre-transplant protocols [23,35,37]. Other studies that assess treatment duration in MDS are, to the best of our knowledge, not available.

In addition to the observed treatment durations, patients with MDS had a poor median OS after discontinuation of treatment, irrespective of treatment type. Other studies have confirmed a poor prognosis after treatment discontinuation [21,29,38–40]. The Kaplan-Meier analyses showed that the median OS appears to be better for patients who received treatment, though not statistically significant. Of note is that reasons why physicians and their patients decide to start treatment are highly individualized. The comparison of the median OS between both groups should therefore be interpreted with care, because the intervention and the selection will both influence the survival outcome. Whether additional treatments appear to benefit patients more than adequate supportive/palliative care is therefore speculative. Our study reports on an older population of patients with MDS with a median age of 74 years, which aligns with other population-based studies, but our cohort is significantly older than the median age reported in clinical trials [10,28,29,40]. The median time to start of initial treatment in our study was 2–4 months after diagnosis (with the exception of lenalidomide), which may be considered relatively quick. As illustrated by our study, clinicians have chosen to treat these patients, but outcomes in treatment duration and OS are relatively poor. Thus, it is important to communicate realistic treatment goals and expectations to patients with MDS. The most important reason for treatment discontinuation was treatment failure, especially in patients treated with HMA. In combination with the poor median OS after treatment discontinuation, this finding highlights the importance of new therapeutic options for older patients with MDS or strategies to optimize the duration of existing treatment options. The limited treatment options for patients with MDS might not be sufficient to augment survival, and previous studies have recommended the improvement of current treatment strategies and development of new therapeutic agents for this population [31]. Unfortunately, clinical trials investigating new agents in older patients with MDS are scarce, and new treatments that greatly improve the prognosis of patients with MDS are yet to be discovered or approved [15,21,29]. Off-label use is permitted by Dutch law under the condition of multidisciplinary consent, which allows physicians to prescribe treatments to patients when they do not fulfill all the criteria for on-label use and can provide them with an additional treatment option [20]. Indeed, our study demonstrates that patients received treatment despite not meeting the conditions, such as a low IPSS-R score for HMA or intensive chemotherapy. This has also been shown in previous studies [22,41]. Prescribing treatments for patients outside the clinical indication again shows the outcomes in a complex disease with limited treatment options. It raises the question of whether further development of protocols

Table 2
Reasons for discontinuation of first line treatment.

	HMA (n = 45)			Intensive chemotherapy (n = 18)			Lenalidomide (n = 4)			ESA (n = 77)			Total (N = 144)
	Lower-risk MDS	Higher-risk MDS	Unknown risk MDS	Lower-risk MDS	Higher-risk MDS	Unknown risk MDS	Lower-risk MDS	Higher-risk MDS	Unknown risk MDS	Lower-risk MDS	Higher-risk MDS	Unknown risk MDS	
Total	20 (100)	19 (100)	6 (100)	9 (100)	3 (100)	6 (100)	4 (100)	0 (0)	0 (0)	49 (100)	7 (100)	21 (100)	
Treatment failure	9 (45.0)	13 (68.4)	4 (66.7)	2 (22.2)	0 (0)	3 (50.0)	0 (0)	0 (0)	0 (0)	20 (40.8)	5 (71.4)	10 (47.6)	66 (45.8)
No/Insufficient response	5 (25.0)	8 (42.1)	2 (33.3)	1 (11.1)	0 (0)	2 (33.3)	0 (0)	0 (0)	0 (0)	16 (32.7)	3 (42.9)	7 (33.3)	44 (30.6)
Disease progression	4 (20.0)	5 (26.3)	2 (33.3)	1 (11.1)	0 (0)	1 (16.7)	0 (0)	0 (0)	0 (0)	4 (8.2)	2 (28.6)	3 (14.3)	22 (15.3)
Toxicity/AE	5 (25.0)	3 (15.8)	0 (0)	0 (0)	0 (0)	0 (0)	2 (50.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	10 (6.9)
Contra-indication	3 (15.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (25.0)	0 (0)	0 (0)	2 (4.1)	1 (14.3)	1 (4.8)	8 (5.6)
Deceased	0 (0)	1 (5.3)	0 (0)	4 (44.4)	1 (33.3)	1 (16.7)	1 (25.0)	0 (0)	0 (0)	15 (30.6)	1 (14.3)	5 (23.8)	29 (20.1)
Other	2 (10.0)	2 (10.5)	2 (33.3)	3 (33.3)	2 (66.7)	2 (33.3)	0 (0)	0 (0)	0 (0)	1 (2.0)	0 (0)	0 (0)	14 (9.7)
Preparation SCT	0 (0)	2 (10.5)	0 (0)	3 (33.3)	2 (66.7) [a]	2 (33.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	9 (6.3)
Patient request	2 (10.0)	0 (0)	1 (16.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (2.1)
Unknown	0 (0)	0 (0)	1 (16.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.0)	0 (0)	0 (0)	2 (1.4)
Not terminated	1 (5.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	11 (22.4)	0 (0)	5 (23.8)	17 (11.8)

Values are presented as number (%) of patients.
Abbreviations: ESA: Erythropoiesis stimulating agent, HMA: Hypomethylating agent, SCT: Stem cell transplantation. [a] One patient initially showed treatment failure on intensive chemotherapy, but received second-line intensive chemotherapy and SCT later on.

is needed or whether hematology is pre-eminently an empirical subject with personalized decisions on the patient level.

The strengths of this study lie in its detailed clinical information. It is the first population-based study to assess real-world treatment patterns for first and consecutive treatments in patients with MDS, as NCR predominantly provides data regarding first-line treatments [17,30,31]. The HemoBase registry ensured a population-based setting for multicenter research over long-term follow-up. The study thus provides insight into treatment duration, treatment discontinuation, and consecutive treatment patterns in a representative, unselected cohort of patients with MDS. These factors have not been studied before in a real-world population of older patients with MDS, and this type of study can be complementary to data from clinical trials [18]. Another strength is that we retrospectively examined the complete medical files for each patient, reflecting the struggle of the treating hematologist to creatively optimize treatment with limited treatment options without influencing the physicians' behavior. This study therefore reflects the real-world situation for treatment of MDS.

A limitation is that outcomes of treatment duration studies may be influenced by the introduction of new therapeutic agents. During follow-up, HMA and lenalidomide were introduced. However, patients with MDS were not treated simultaneously with these treatments, nor were HMA and lenalidomide considered competitive treatments to each other. The introduction of HMA and lenalidomide was therefore not expected to affect the treatment duration of other treatments. In addition, we were unable to study the clinical data of blood and bone marrow samples to examine response to treatment. Therefore, conclusions about the response to treatment should be studied in prospective trials [26,27]. This study solely examined the duration of treatment, consecutive treatment patterns, and reasons for treatment discontinuation in patients with MDS.

In conclusion, this population-based study comprising a complete 13-year cohort of older patients with MDS showed that about half of the population of patients with MDS received treatment. Few patients received consecutive treatment, and treatment failure was the most important reason for treatment discontinuation. Treatment duration in patients with MDS was relatively limited, and once initial treatment was abrogated, median OS was half a year. Because of the paucity of treatment options for patients with MDS, it is vital to maintain the initial treatment as long as possible. This study shows the outcomes in a real-world population of older patients with MDS. There is still an urgent need for new therapeutic agents and treatment options, for strategies to further optimize the duration of existing treatment options, and for communicating realistic expectations regarding treatment goals and outcomes to patients, especially older, higher-risk patients with MDS with a poor prognosis.

Ethics Approval and Consent to Participate

The Medical Ethics Committee in Leeuwarden (Regionale Toetsingscommissie Patiëntgebonden Onderzoek, Leeuwarden, the Netherlands) confirmed a conduct of the retrospective study without the need for ethical review, and the institutional boards approved the execution of the study without the need for consent in accordance with the Declaration of Helsinki (2013 revision) and Dutch regulations.

Consent for Publication

All authors have given consent for publication.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Funding

Not applicable.

Authors' Contributions

JR, JG, ER, MH, RK designed the project. JR and JG collected the data. JR wrote the manuscript. JR, JG and NV analyzed the data. ER, MH, RK and NV provided input in data analysis. All authors contributed to critical revision and gave final approval of the manuscript.

Declaration of Competing Interest

All authors declare no competing financial interests.

Acknowledgements

The authors would like to thank Petra Meestringa (Nij Smellinghe, Drachten, the Netherlands) for the support in data collection; Jisk Koopmans (Certe Medical Diagnostics & Advice, Leeuwarden, the Netherlands) for revision of bone marrow specimens; and the Frisian hospitals for their cooperation.

HemoBase Population Registry Consortium: Antonius Sneek, Hematology: Gerrit Jan Veldhuis, Gerhard Woolthuis, Leonie van der Burg; Tjongerschans Heerenveen, Hematology: Bas van Rees; Medical Center Leeuwarden, Hematology: Mels Hoogendoorn, Bas Franken, Esther de Waal, Rozemarijn van Rijn, Peter Joosten, Hilde van der Galiën; Medical Center Leeuwarden, Clinical Pharmacy & Pharmacology: Eric van Roon, Berdien Oortgiesen, Hanne Rozema; Medical Center Leeuwarden, MCL Academy: Nic Veeger; Nij Smellinghe Drachten, Hematology: Sjoerd Hovenga, Frank Schipper, Harmen van Kamp; Nij Smellinghe Drachten, Klinical Chemistry: Adrian Kruit; Certe Medical Diagnostics & Advice: Huib Storm, Harry de Wit, Willeke Ferket-Franken; Radiotherapy Institute Friesland: Wilma Smit, Renske Vlasman; Pathology Friesland: Robby Kibbelaar, Roy Jurhill, Sophie Dijkhuizen, Elise van der Logt; University Medical Center Groningen, Genetics, Genome Diagnostics: Eva van den Berg-de Ruiter.

References

[1] Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391–405.
[2] McQuilten ZK, Wood EM, Polizzotto MN, et al. Underestimation of myelodysplastic syndrome incidence by cancer registries: Results from a population-based data linkage study. Cancer. 2014;120(11):1686–94.
[3] Moreno Berggren D, Folkvaljon Y, Engvall M, et al. Prognostic scoring systems for myelodysplastic syndromes (MDS) in a population-based setting: a report from the Swedish MDS register. Br J Haematol 2018;181(5):614–27.
[4] Nachtkamp K, Stark J, Kündgen A, et al. Eligibility for clinical trials is unsatisfactory for patients with myelodysplastic syndromes, even at a tertiary referral center. Leuk Res 2021;108:106611.
[5] Carraway HE, Saygin C. Therapy for lower-risk MDS. Hematology Am Soc Hematol Educ Program 2020;2020(1):426–33.
[6] Ferrara F, Bernardi M. 2021 BSH guidelines for the management of adult myelodysplastic syndromes: a practical approach to a challenging disease. Br J Haematol 2021;194(2):235–7.
[7] Greenberg PL, Stone RM, Al-Kali A, et al. NCCN guidelines® insights: myelodysplastic syndromes, version 3.2022. J Natl Compr Canc Netw 2022;20(2):106–17.
[8] Bewersdorf JP, Zeidan AM. Management of patients with higher-risk myelodysplastic syndromes after failure of hypomethylating agents: What is on the horizon? Best Pract Res Clin Haematol 2021;34(1):101245.
[9] Zeidan AM, Hu X, Zhu W, et al. Association of provider experience and clinical outcomes in patients with myelodysplastic syndromes receiving hypomethylating agents. Leuk Lymphoma 2019;1–12.
[10] Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol 2009;10(3):223–32.
[11] Bernal T, Martinez-Camblor P, Sanchez-Garcia J, et al. Effectiveness of azacitidine in unselected high-risk myelodysplastic syndromes: results from the Spanish registry. Leukemia. 2015;29(9):1875–81.
[12] Bewersdorf JP, Zeidan AM. Evolving therapies for lower-risk myelodysplastic syndromes. Ann Hematol 2020;99:677–92.
[13] Stein EM, Bonifacio G, Latremouille-Viau D, et al. Treatment patterns and outcomes in patients with myelodysplastic syndromes treated with hypomethylating agents: a SEER-Medicare analysis. Leuk Lymphoma 2021;1–16.
[14] Balleari E, Salvetti C, Del Corso L, et al. Age and comorbidities deeply impact on clinical outcome of patients with myelodysplastic syndromes. Leuk Res 2015;39(8):846–52.
[15] Duetz C, Cucchi DGJ, Polak TB, et al. The wider perspective: twenty years of clinical trials in myelodysplastic syndromes. Br J Haematol 2021;196:329–35.
[16] Medicines - European Medicine Agency [Internet] [cited 06 December 2021]. Available from: https://www.ema.europa.eu/en/medicines/field_ema_web_categories%253Aname_field/Human/ema_group_types/ema_medicine; 2021.
[17] Dinmohamed A, Brink M, Dinnessen M, Durmaz M, Oerlemans S, Korf van Vliet C. Hemato-oncologische Zorg in Nederland. IKNL; 2021.
[18] Kibbelaar RE, Oortgiesen BE, van der Wal-Oost AM, et al. Bridging the gap between the randomised clinical trial world and the real world by combination of population-based registry and electronic health record data: A case study in haemato-oncology. Eur J Cancer 2017;86:178–85.
[19] Rozema J, Hoogendoorn M, Kibbelaar R, van den Berg E, Veeger N, van Roon E. Comorbidities and malignancies negatively affect survival in myelodysplastic syndromes: a population-based study. Blood Adv 2021;5(5):1344–51.
[20] Wetten.overheid.nl.art. 68 Geneesmiddelenwet. Geneesmiddelenwet. 2021.
[21] Garcia-Manero G, Chien KS, Montalban-Bravo G. Myelodysplastic syndromes: 2021 update on diagnosis, risk stratification and management. Am J Hematol 2020;95(11):1399–420.
[22] Kasprzak A, Nachtkamp K, Kondakci M, et al. Analysis of the impact of adherence to guidelines and expert advice in patients with myelodysplastic syndromes. Ann Hematol 2021;100(2):455–63.
[23] Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood. 2012;120(12):2454–65.
[24] van den Reek JMPA, Kievit W, Gniadecki R, et al. Drug Survival Studies in Dermatology:Principles, Purposes, and Pitfalls. J Invest Dermatol 2015;135(7):1–5.
[25] Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood. 2006;108(2):419–25.
[26] Carrascosa JM, Notario J. Drug survival in biologic therapy. Do we know what it means? Can we calculate it? Actas Dermosifiliogr 2014;105(8):729–33.
[27] van den Reek JMPA, Kievit W, de Jong EMGJ. Comment on "Drug survival analysis is not a good method for assessing the safety or effectiveness of systemic therapies in psoriasis". Actas Dermosifiliogr 2017;108(7):695–6.
[28] Tsutsué S, Suzuki T, Kim H, Crawford B. Real-world assessment of myelodysplastic syndrome: Japanese claims data analysis. Future Oncol 2021;18:93–104.
[29] Park S, Hamel JF, Toma A, et al. Outcome of lower-risk myelodysplastic syndrome with ring sideroblasts (MDS-RS) after failure of erythropoiesis- stimulating agents. Leuk Res 2020;99:106472.
[30] Lauritsen TB, Nørgaard JM, Grønbæk K, et al. The Danish myelodysplastic syndromes database: patient characteristics and validity of data records. Clin Epidemiol 2021;13:439–51.
[31] Dinmohamed AG, Visser O, van Norden Y, et al. 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;50(5):1004–12.
[32] Jacobsen AM, Poynter JN, Richardson MR, et al. Factors predicting early mortality after new diagnosis of myelodysplastic syndrome: a population-based study. Eur J Haematol 2019;103(1):56–63.
[33] Singhal D, Kutyna MM, Chhetri R, et al. Red cell alloimmunization is associated with development of autoantibodies and increased red cell transfusion requirements in myelodysplastic syndrome. Haematologica. 2017;102(12):2021–9.
[34] Platzbecker U. Treatment of MDS. Blood. 2019;133(10):1096–107.
[35] van de Loosdrecht AA, Huls G, Wijermans P, et al. Myelodysplastic syndromes: guidelines for therapy 2013 *Nederlands Tijdschrijft voor*. Hematologie. 2013;10(2):43.
[36] Malcovati L, Hellström-Lindberg E, Bowen D, et al. Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet. Blood. 2013;122(17):2943–64.
[37] Saygin C, Carraway HE. Current and emerging strategies for management of myelodysplastic syndromes. Blood Rev 2021;48:100791.
[38] Cabrero M, Jabbour E, Ravandi F, et al. Discontinuation of hypomethylating agent therapy in patients with myelodysplastic syndromes or acute myelogenous leukemia in complete remission or partial response: retrospective analysis of survival after long-term follow-up. Leuk Res 2015;39(5):520–4.
[39] Jabbour E, Garcia-Manero G, Batty N, et al. Outcome of patients with myelodysplastic syndrome after failure of decitabine therapy. Cancer. 2010;116(16):3830–4.
[40] Zeidan AM, Salimi T, Epstein RS. Real-world use and outcomes of hypomethylating agent therapy in higher-risk myelodysplastic syndromes: Why are we not achieving the promise of clinical trials? Future Oncol 2021;17:5163–75.
[41] Zeidan AM, Jayade S, Schmier J, et al. Injectable hypomethylating agents for management of myelodysplastic syndromes: patients' perspectives on treatment. Clin Lymphoma Myeloma Leuk 2021;22:e185–98.