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## RESEARCH ARTICLE

# Causes of early death and treatment-related death in newly diagnosed pediatric acute myeloid leukemia: Recent experiences of the Dutch Childhood Oncology Group

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## Abstract

**Background:** With the current more effective treatment regimens for pediatric acute myeloid leukemia (AML), research on early death (ED), treatment-related mortality (TRM), and toxicity becomes increasingly important. The aim of this study was to give an overview of the frequency, clinical features, and risk factors associated with ED and TRM in first complete remission (CR1) during the last three consecutive treatment protocols of the Dutch Childhood Oncology Group (DCOG) between 1998 and 2014.

**Methods:** Incidence and risk factors associated with ED and TRM in CR1 were retrospectively studied in 245 patients treated according to the Dutch ANLL-97/AML-12 ( $n = 118$ ), AML-15 ( $n = 60$ ), or DB AML-01 ( $n = 67$ ) protocols.

**Results:** The incidence of ED was, respectively, 5.1%, 6.7%, and 3.0% excluding deaths before treatment ( $P = \text{NS}$ ), and 7.4%, 11.1%, and 4.4% including deaths before the onset of treatment. Severe underweight at initial diagnosis was significantly associated with more frequent ED. When relapse was included as a competing risk, cumulative incidence of death in CR1 were 5.9%, 5.0%, and 4.6% for ANLL97, AML15, and DB01, respectively ( $P = \text{NS}$ ). The most important cause of TRM included infectious and SCT-related complications.

**Conclusion:** We report relatively stable rates of ED and TRM in CR1 in the latest completed DCOG protocols for newly diagnosed AML patients. The most important causes of TRM were SCT- or infection-related, warranting further evaluation and awareness.

## KEYWORDS

death in CR1, outcome, pediatric acute myeloid leukemia/pediatric AML, toxicity, treatment-related mortality

Abbreviations: (allo-)SCT, (allogeneic) Stem cell transplantation; (p)EFS, (probability of) event-free survival; (p)OS, (probability of) overall survival; (v)ED, (very) early death; AML, acute myeloid leukemia; CBF, core-binding factor; CNS, central nervous system; CR(1), (first) complete remission; CRM, chemotherapy-related mortality; DCOG, Dutch Childhood Oncology Group; FAB type, French-American-British type; IC, informed consent; MRD, minimal residual disease; NS, nonsignificant; SDS BMI, standardized body mass index; SE, standard error; TRM, treatment-related death; WBC, white blood cell count.

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## 1 | INTRODUCTION

With the current more effective treatment regimens for pediatric acute myeloid leukemia (AML),<sup>1,2</sup> early death (ED), treatment-related mortality (TRM), therapy-related side effects, quality of life, and cost-efficiency become increasingly important fields of research. Although TRM has decreased substantially over the past years, approximately 3% to 15% of the patients in first complete remission (CR1) still die due to treatment-related toxicity.<sup>3-7</sup> Over a decade ago, Slats et al.<sup>3</sup> reported a significant decline of ED rates within the pediatric AML protocols of the Dutch Childhood Oncology Group (DCOG), with an incidence of 27% in AML-82, decreasing to 10% in AML-92/94. However, chemotherapy-related mortality (CRM) of patients in CR1 increased from 1% in AML-87 to 3% in AML-82 and 8% in the AML-92/94 protocol. Infections were the leading cause of death, followed by intracerebral hemorrhage and nonspecified multiorgan failure. Similar percentages were reported for the earlier protocols by other international groups, but, contrary to the DCOG protocols, during their consecutive protocols, CRM generally decreased.<sup>4-8</sup> Therefore, the aim of this study was to give an overview of the frequency, clinical features, and possible risk factors associated with ED and TRM during the last three consecutive AML treatment protocols of the DCOG.

## 2 | METHODS

### 2.1 | Patients

Patients, aged 0 to 19 years, with AML, newly diagnosed between 1998 and 2014 and participating in one of the following DCOG protocols—ANLL-97/MRC AML-12 (ANLL97; 1998-2002), AML-15 (AML15; 2002-2009), DB AML-01 (DB01; 2009-2014)<sup>9</sup>—were eligible for inclusion. Written informed consent (IC) by the patient and/or parents/guardians for the use of information for study purposes (normally implemented in the overall IC of the applicable protocols) had to be present. Patients who died prior to IC of the protocol could not be included. However, the number of patients with death before inclusion is registered by the DCOG and was queried separately. Patients with acute promyelocytic leukemia, myeloid leukemia of Down syndrome, or secondary AML were excluded.

After a list with eligible patients was provided by the DCOG, coordinating members of the study team contacted the (at that time) seven treating Dutch pediatric oncology centers. Medical records of all patients eligible for inclusion were reviewed on site by members of the study team between January 2016 and June 2018. Baseline characteristics, treatment details, outcomes, including causes of death, and follow-up were structurally documented in patient-specific case report forms. In case of missing baseline data in the chart, the DCOG database was checked to complement the information. Toxicity data and details on the cause of death were collected during initial treatment until the patient had recovered from the last episode of neutropenia, until progression to relapse/refractory treatment, or until the date of allogenic stem cell transplantation (allo-SCT), if applicable.

Causes of death in refractory and/or relapsed patients were registered, but not included in the main analyses of this article. Allo-SCT-related death was registered, but details on SCTs were beyond the scope of this study. Response measures and events were adopted from the DCOG database. Follow-up data with regard to events was collected for all patients until the last date of follow-up closed to the study visit date or until the date of death.

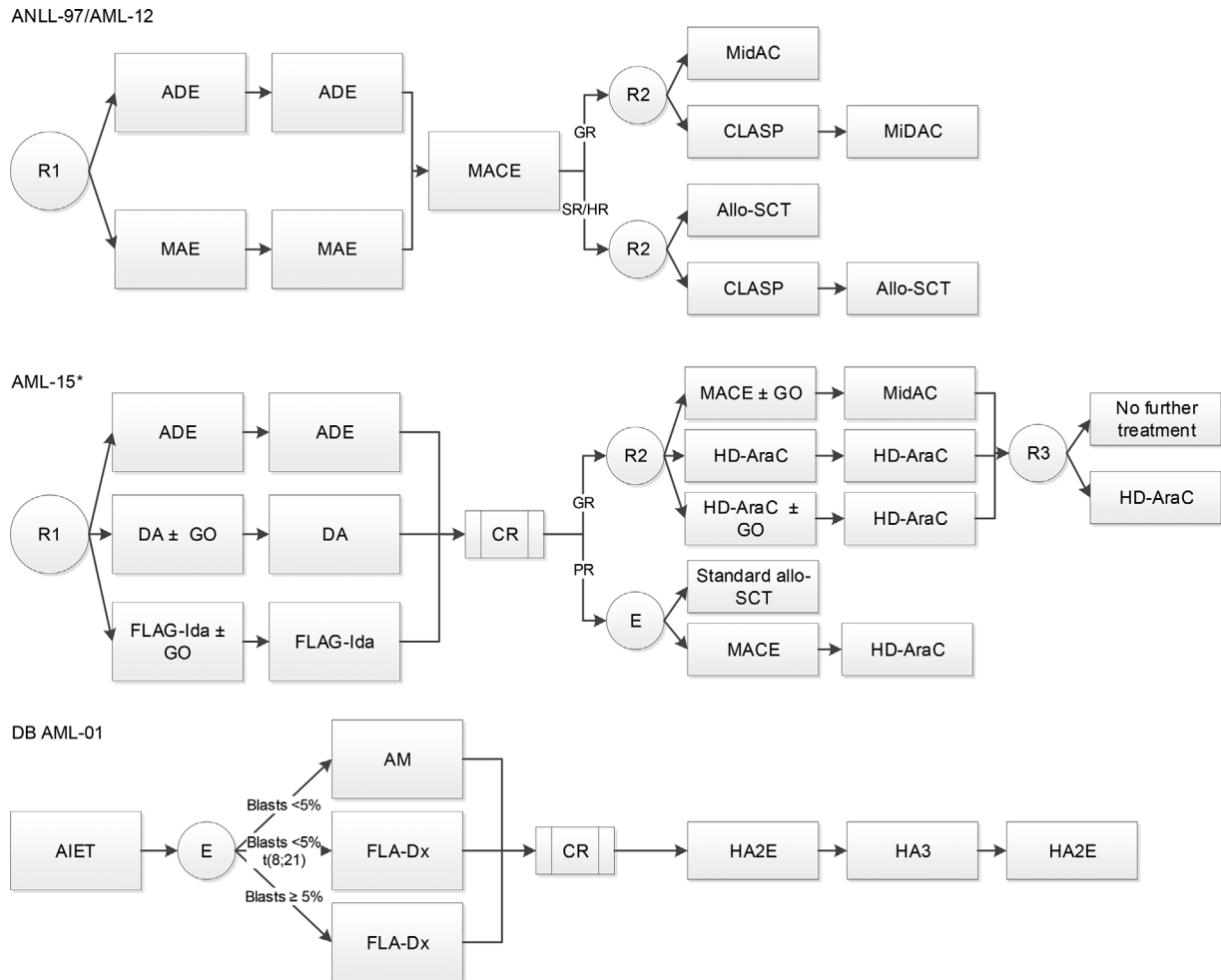
This study was approved by the DCOG's research committee and the Ethical Committee at VU University Medical Center, Amsterdam, the Netherlands.

### 2.2 | Treatment

Like other international protocols, the Dutch treatment protocols all had a backbone of cytarabine and anthracyclines. Figure 1 gives a schematic overview of the included treatment protocols and Supporting Information Table S1 gives a comprehensive overview of the agents and doses used per protocol. Supportive care guidelines were described in the protocols. All protocols prescribed hyperhydration at the start of the treatment, but the use of either allopurinol or rasburicase was not standardized. All patients were prescribed antibiotic prophylaxis with co-trimoxazole against *Pneumocystis Jirovecii* pneumonia. Additional selective gut decontamination (first two protocols) or systemic prophylaxis with (fluoro)quinolones (i.e., ciprofloxacin; this was officially implemented in the last protocol, but many centers already started this halfway the previous protocol) was given during episodes of neutropenia, but various regimens were center specific. All centers prescribed antifungal prophylaxis, mostly with oral itraconazole (liquid). Patients with suspected infections were treated according to local hospital guidelines.

### 2.3 | Definitions and risk factors

Definitions in respect to treatment response were adopted from an international pediatric AML expert panel.<sup>10</sup> Complete remission (CR) was defined as bone marrow blasts below 5% in absence of blasts with Auer rods and absence of extramedullary disease, in presence of signs of bone marrow recovery.<sup>10</sup> Overall survival (OS) was defined as the time elapsed between the date of diagnosis and the date of death or the date of last follow-up. Event-free survival (EFS) was defined as the time elapsed between the date of diagnosis and the date of the first event (i.e., failure to achieve CR, relapse, death, secondary malignancy) or date of last follow-up in absence of an event. Relapse was defined as reappearance of bone marrow blasts  $\geq 5\%$  or malignant blasts in the blood, or development of extramedullary disease. Patients who died before day 42 were considered EDs.<sup>10</sup> ED was defined as death in induction before CR was achieved. Patients who died after achieving CR after one course, but died during the second course after day 42 were considered deaths in CR1 (even though they did not complete the whole induction). Very early death (vED) was defined as death in the first two weeks (days 1-15) of treatment. TRM was defined as any death in CR1 (without evidence of emerging relapse),<sup>4-6</sup> including all forms of treatment including allo-SCT in CR1. An elaborate overview



**FIGURE 1** Overview of included treatment protocols

\*The DCOG did not participate in the randomization for GO and randomization three in AML15.

Abbreviations: ADE, Ara-C, daunorubicin, etoposide; AIET, Ara-C, idarubicin, etoposide, 6-TG; allo-SCT, allogenic stem cell transplantation; AM, Ara-C, mitoxantrone; Ara-C, cytosine arabinoside; auto-SCT, autologous stem cell transplantation; CLASP, HD-AraC, L-asparaginase; CR, complete remission; DA, daunorubicin, Ara-C; E, evaluation; FLA-Dx, fludarabine, HD-AraC, liposomal daunorubicin; FLAG-Ida, fludarabine, HD-AraC, granulocyte colony stimulating factor; idarubicin; GO, gemtuzumab ozogamicin; HA2E, HD-AraC, etoposide; HA3, HD-AraC; HA3E, HD-AraC, etoposide; HAM, HD-AraC, mitoxantrone; HD-AraC, high-dose Ara-C; MACE, amascrine, Ara-C, etoposide; MAE, mitoxantrone, Ara-C, etoposide; MidAC, mitoxantrone, Ara-C; PR, poor risk; R, randomization; SR, standard risk

of allo-SCT-related mortality and associated risk factors was beyond the scope of this study. CRM was defined as death in CR1 during initial treatment with chemotherapy until 6 weeks after the last course, excluding events occurring after allo-SCT.

Infections were microbiologically proven (in case of blood stream infections or sepsis) and/or defined by the treating physician based on clinical, laboratory, and/or radiographical findings.

Patients with a very early relapse during treatment were taken into account until the moment of relapse. Risk factors for TRM and CRM were studied only in patients who achieved CR1. Studied risk factors for ED and death in CR1 included age, sex, standardized body mass index (SDS BMI) at time of diagnosis according to the TNO Netherlands organization for applied scientific research (<https://tnochildhealthstatistics.shinyapps.io/JGZRIchtlijnLengtegroei/>), with underweight defined as  $\leq -2$  SDS and overweight defined as  $\geq +2$  SDS BMI and severe underweight defined as  $\leq -3$  SDS and severe

overweight defined as  $\geq +3$  SDS BMI (due to low numbers not applied in cumulative incidence of TRM analyses), morphological classification, i.e., French-American-British (FAB) type, white blood cell count (WBC), central nervous system (CNS) involvement, cytogenetics categorized as core-binding factor (CBF) leukemia [t(8;21)(q22;q22) or inv(16)/t(16;16)(p13q22)] or other, and treatment protocol. CNS involvement was defined as CNS2 or CNS3, because in the earliest protocols no distinction between the two was made. Undefined traumatic lumbar punctures were excluded from these analyses.

## 2.4 | Statistical analyses

Associations between clinical characteristics and subgroups were evaluated using the Student *t* test (normal distribution) or the nonparametric Mann-Whitney *U* test (nonnormal distribution) for continuous variables and the  $\chi^2$  test or Fisher exact test for categorical variables.

Associations between clinical characteristics and multiple subgroups were determined using the one-way ANOVA test with a post-hoc test (Bonferroni; normal distribution) or the Kruskal-Wallis test (nonnormal distribution) for continuous variables and with univariate logistic regression analysis for multiple dichotomous variables. The Kaplan-Meier method was used to estimate (event-free) survival probabilities and subgroups were compared using a log-rank test.

Although patient numbers were small, cumulative incidences of TRM were calculated, with ED and refractory disease (both by definition) and relapse disease as competing events. Incidences at time point = 2 years are shown. Unadjusted TRM numbers are also shown to enable comparison with previous numbers reported by the DCOG. All risk factors were univariately studied in relation to both unadjusted TRM incidence numbers and cumulative incidence numbers.

Two-sided *P* values of < 0.05 were considered statistically significant. Analyses were conducted using SPSS software 23.0 and R studio, version 3.5.3.

### 3 | RESULTS

In total, 245 patients were included, of which 118 patients (48%) were treated according to ANLL97, 60 patients (24%) according to AML15, and 67 patients (27%) according to DB01. Table 1 shows the clinical characteristics of the study population. There were no statistically significant differences between baseline characteristics among the three protocols.

The one-year/five-year probability of EFS (pEFS) was 60% (SE, 5%)/45% (SE, 5%), 63% (SE, 6%)/49% (SE, 7%), and 65% (SE, 6%)/48% (SE, 6%) for ANLL97, AML15, and DB01, respectively (all  $P_{\text{overall}} = \text{NS}$ ). The one-year/five-year probability of OS (pOS) was 78% (SE, 4%)/57% (SE, 5%), 82% (SE, 5%)/61% (SE, 6%), and 86% (SE, 4%)/72% (SE, 6%), respectively (all  $P_{\text{overall}} = \text{NS}$ ). In total, 12 patients died early (4.9%). ED was respectively 5.1% ( $n = 6$ ), 6.7% ( $n = 4$ ), and 3.0% ( $n = 2$ ) excluding deaths before treatment ( $P = \text{NS}$ ). Three included patients died before day 15 (1.2%). In the given time period, another seven patients died prior to the onset of treatment according to the DCOG database. For these patients, no IC was available; thus, clinical information was lacking. If these patients were included in the number of EDs, the total ED rate was 7.5% ( $n = 19$ ) for the total cohort, and 7.4% ( $n = 9$ ), 11.1% ( $n = 7$ ), and 4.4% ( $n = 3$ ) for the protocols ANLL97, AML15, and DB01, respectively ( $P = \text{NS}$ ) (Table 2).

Of the 219 patients (89%) who initially achieved CR1 (see Supporting Information Table S2 for patient characteristics), seven patients (3.2%) died in CR1. Median follow-up time among patients who achieved CR1 was 4.3 (1.6-9.5) years. In ANLL97, AML15, and DB01, TRM not including competing events was 3.8%, 1.9%, and 3.2%, respectively ( $P = \text{NS}$ ). Unadjusted CRM in CR1 ranged from 2.9% in ANLL97 to 1.6% in DB01 ( $P = \text{NS}$ ) (see Supporting Information Figure S2). Cumulative incidences of TRM were 5.9% (SE, 2.2%), 5.0% (SE, 2.8%), and 4.6% (SE, 2.6%) for ANLL97, AML15, and DB01, respectively ( $P = \text{NS}$ ) (see Figure 2).

Two patients (one in ANLL97, and, although SCT in CR1 was not prescribed by the protocol, one in DB01) died from complications after SCT in CR1. Causes of death among patients who died of non-SCT-related causes in CR1 included mainly infectious complications ( $n = 1$  septic shock,  $n = 1$  meningitis and neurotoxicity,  $n = 1$  pulmonary bleeding due to invasive Aspergillosis). One patient was reported with death due to several complications, including candida sepsis, veno-occlusive disease and ultimately multiorgan failure. One patient died as a result of cardiotoxicity (i.e., dilatating cardiomyopathy).

An overview of cases of ED and TRM and deaths per treatment phase is shown in Table 3 and Supporting Information Figure S1, respectively.

#### 3.1 | Risk factors

Ten male patients (7.0%) died early, compared with two females (1.9%) ( $P = 0.079$ ). Age was not significantly associated with ED, nor were age categories (below or under the age of 2, 10, or 12 years)<sup>4</sup> (all  $P = \text{NS}$ ). SDS BMI was, as a continuous variable, not associated with ED ( $P = \text{NS}$ ). Underweight defined as  $\leq 2$  SDS was not significantly associated with ED. ED rates in patients with severe underweight ( $n = 2$ ) were significantly higher than in patients with BMI SDS higher than  $-3$  ( $n = 9$ ) (18% vs 2%,  $P = 0.029$ ). WBC was not associated with ED, nor were hyperleukocytosis (i.e.,  $\geq 100 \times 10^9/\text{L}$  at diagnosis), FAB type, CNS involvement, or CBF abnormalities (all  $P = \text{NS}$ ).

Among patients who achieved CR1, age below two year was associated with more unadjusted TRM (8.3% vs 1.3%,  $P = 0.018$ ) in simple univariate analysis, but this was not confirmed when using competing risk analyses. None of the other covariates was significantly associated with death in CR1 in either simple univariate analyses or competing risk analyses. Results were similar for CRM (data not shown).

### 4 | DISCUSSION

Over the past decades, the ED rate (including deaths before treatment) in Dutch protocols decreased to 4% in the latest completed protocol, DB01. This is in line with numbers reported by others.<sup>4-6,8,11</sup> Slats et al.<sup>3</sup> reported an increase in CRM in previous Dutch protocols, but this fortunately was not sustained in the later protocols. Incidences of both ED and TRM did not significantly decrease in our cohort. As previously reported, Dutch CRM/TRM incidences were calculated without competing events<sup>3</sup>; we can only compare our unadjusted incidence numbers. Although this might suggest a decrease in TRM and a further decline in ED rate for the latest protocols, we are not able to compare these incidence numbers statistically. Our cumulative incidences of death in CR1 are similar to those reported by other study groups in overlapping time periods.<sup>4-6,8,11,12</sup> However, comparing TRM rates is cumbersome due to the lack of uniformly used definitions.<sup>13,14</sup> Because we defined TRM as death in CR1, patients who died in early stages of the treatment as a result of toxicity, but before achieving CR "by definition", are not included in this number. Subsequently, this might be an underestimation compared with other reported TRM

**TABLE 1** Patient characteristics per protocol

	Total N = 245	ANLL-97/AML-12 N = 118 (48)	AML-15 N = 60 (24)	DB AML-01 N = 67 (27)
<b>Characteristics</b>				
Age at diagnosis (y)	6.4 [1.8-12.6]	7.0 [2.0-12.8]	6.5 [1.8-12.1]	6.1 [1.4-11.7]
<2	65 (27)	29 (25)	16 (27)	20 (30)
≥2	180 (74)	89 (75)	44 (73)	47 (70)
Male	142 (58)	72 (61)	36 (60)	34 (51)
Female	103 (42)	46 (39)	24 (40)	33 (49)
SDS BMI at diagnosis <sup>a</sup> (n = 227)	-0.1 ± 1.5	-0.2 ± 1.6	-0.2 ± 1.2	0.1 ± 1.5
<b>Underweight</b>				
SDS BMI ≤ -3	6 (3)	5 (5)	1 (2)	0
SDS BMI > -3	221 (97)	105 (96)	57 (98)	59 (100)
SDS BMI ≤ -2	21 (9)	14 (13)	2 (3)	5 (9)
SDS BMI > -2	206 (91)	96 (87)	56 (97)	54 (92)
<b>Overweight</b>				
SDS BMI ≥ +2	18 (8)	8 (7)	2 (3)	8 (14)
SDS BMI < +2	209 (92)	102 (93)	56 (97)	51 (86)
SDS BMI ≥ +3	5 (2)	3 (3)	0	2 (3)
SDS BMI < +3	222 (98)	107 (97)	58 (100)	57 (97)
WBC at diagnosis (×10 <sup>9</sup> /L) (n = 241)	19 [6-77]	19 [8-93]	16 [3-51]	21 [11-88]
<50	170 (71)	78 (68)	45 (75)	47 (71)
≥50	70 (29)	36 (32)	15 (25)	19 (29)
<100	188 (78)	87 (76)	50 (83)	51 (77)
≥100	52 (22)	27 (24)	10 (17)	15 (23)
<b>FAB type (n = 233)</b>				
M0	21 (9)	11 (10)	6 (10)	4 (7)
M1	31 (13)	16 (14)	6 (10)	9 (16)
M2	42 (17)	22 (19)	13 (22)	7 (12)
M4	50 (20)	27 (23)	12 (20)	11 (19)
M4eo	9 (4)	3 (3)	2 (3)	4 (7)
M5	58 (24)	26 (22)	14 (24)	18 (31)
M6	2 (1)	0	1 (2)	1 (2)
M7	20 (8)	11 (10)	5 (9)	4 (7)
<b>Cytogenetics (n = 225)</b>				
CBF abnormalities	53 (24)	25 (23)	13 (23)	15 (25)
Other	172 (76)	83 (77)	43 (77)	46 (75)
CNS involvement <sup>b</sup> (n = 220)	60 (27)	30 (29)	9 (17)	21 (33)
No CNS involvement	160 (73)	74 (71)	44 (83)	42 (67)
<b>Treatment aspects</b>				
Allo-SCT in CR1 (n = 243)	14 (6)	9 (8)	3 (5)	2 (3) <sup>c</sup>

Abbreviations: CBF, core-binding factor [including t(8;21)(q22;q22) and inv(16)/t(16;16)(p13q22)]; CNS, central nervous system; CR1, first complete remission; NA, not applicable; (Allo)SCT, allogeneic stem cell transplantation; SDS BMI, standardized body mass index; y, years.

Note. Normally distributed values of continuous variables are expressed as mean ± standard deviation, and other values are expressed as median [25th-75th percentiles]. Categorical variables are expressed in numbers (%). In case of missing data for specific characteristics, the number of patient with available data is shown in brackets; percentages were calculated without "unknown." Percentages may not total 100% due to rounding.

<sup>a</sup>SDS weight to height for children <2 years of age.

<sup>b</sup>CNS involvement was defined as CNS2 or CNS3 according to the DCOG database. Patients with undefined traumatic lumbar puncture status were excluded.

<sup>c</sup>SCT in CR1 was not prescribed by the protocol.



**TABLE 2** Overview of incidences of events per protocol for the patients both included in the study and those registered at the DCOG

DCOG registry, including patients with death before treatment	Total (n = 252), n (%)	ANLL-97/AML-12 (n = 121), n (%)	AML-15 (n = 63), n (%)	DB AML-01 (n = 68), n (%)
Death before treatment	7	3	3	1
ED including deaths before treatment	19 (8)	9 (7)	7 (11)	3 (4)
Study population, excluding patients with death before treatment	Total (n = 245), n (%)	ANLL-97/AML-12 (n = 118), n (%)	AML-15 (n = 60), n (%)	DB AML-01 (n = 67), n (%)
ED	12 (5)	6 (5)	4 (7)	2 (3)
Day 1-15	3 (1)	2 (2)	0	1 (2)
Patients achieving CR1 <sup>a</sup>	219 (89)	103 (87)	53 (88)	63 (94)
TRM in CR1 <sup>b</sup>	7 (3)	4 (4)	1 (2)	2 (3)
CRM in CR1 <sup>b</sup>	5 (2)	3 (3)	1 (2)	1 (2)
Allo-SCT in CR1 (information available in n = 244)	14 (6)	9 (9)	3 (6)	2 (3)
Death after allo-SCT in CR1	2	1	0	1
Number of relapses after CR1	97 (44)	47 (45)	23 (43)	27 (43)
Relapses during treatment	6	3	1	2
Death after relapse <sup>c</sup>	69 (67)	39 (80)	17 (71)	13 (46)*
Patients with RD <sup>d</sup>	17 (7)	10 (9)	5 (8)	2 (3)
Death after RD	6 (35)	3 (30)	2 (40)	1 (50)
Cumulative incidence of TRM <sup>e</sup> [SE]	NA	5.9 [2.2]	5.0 [2.8]	4.6 [2.6]
Outcome				
1y pEFS [SE] <sup>f</sup>	0.62 [0.03]	0.60 [0.05]	0.63 [0.06]	0.65 [0.06]
5y pEFS [SE] <sup>f</sup>	0.47 [0.03]	0.45 [0.05]	0.49 [0.07]	0.48 [0.06]
1y pOS [SE]	0.81 [0.03]	0.78 [0.04]	0.82 [0.05]	0.86 [0.04]
5y pOS [SE]	0.62 [0.03]	0.57 [0.05]	0.61 [0.06]	0.72 [0.06]

Abbreviations: allo-SCT, allogenic stem cell transplantation; CR1, first complete remission; CRM, chemotherapy-related mortality; ED, early death; NA, not applied; pEFS, probability of event-free survival; pOS, probability of overall survival; TRM, treatment-related mortality in CR1; RD, refractory disease; SE, standard error; y, year.

\* $P < 0.05$ .

<sup>a</sup>Patients with ED were considered CR failures, but not as having RD; percentage calculated excluding patients with ED.

<sup>b</sup>Percentage calculated from the total number of patients who achieved CR1 (calculated without taking into account time or competing events).

<sup>c</sup>Percentage calculated from the total number of patients who relapsed after initially achieving CR1 or during treatment.

<sup>d</sup>Percentage calculated from the total number of patients who were diagnosed with RD.

<sup>e</sup>Cumulative incidence of TRM in CR1 at  $t = 2$  year with relapse, RD (by definition), and ED (by definition) as competing event. ED was considered CR failure.

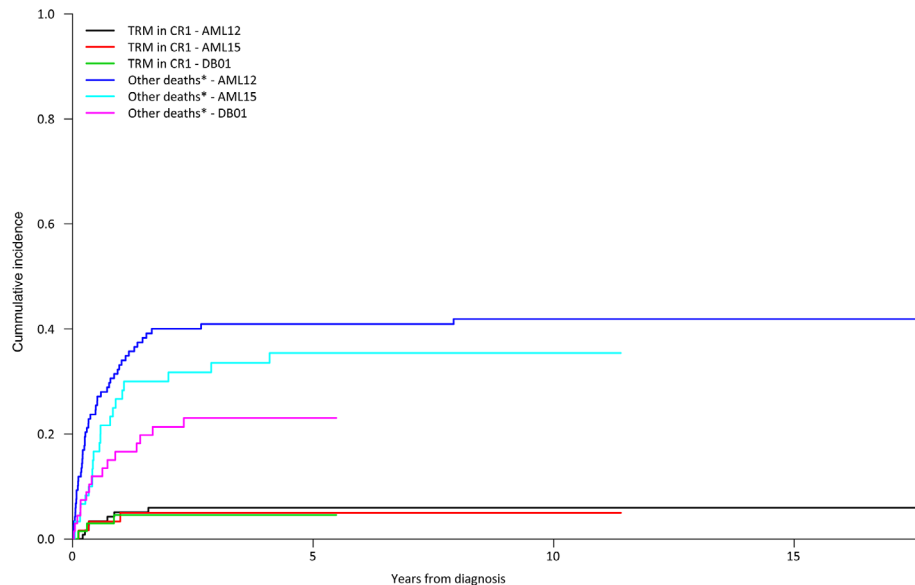
<sup>f</sup>Not achieving CR was considered an event at time point 0.

rates that include patients with just absence of progressive disease at time of death.<sup>14</sup> A very recent study reported that TRM, defined as death in the absence of progressive disease, accounts for more than half of all deaths in Dutch pediatric patients with hematological malignancies.<sup>15</sup>

The most important causes of ED included persistent or progressive disease and infectious complications. The incidence of brain hemorrhage was relatively low in our cohort, but total patient numbers with ED were small, and we were insufficiently informed on causes of death of patients who died prior to the onset of treatment. Causes of ED may be hard to define as ongoing disease contributes to other potential problems during treatment, might result in treatment adaptation with subsequent impact, and influences toxicity.<sup>13</sup> This probably all contributes to the relatively high number of toxic deaths during induction, compared with TRM in CR1. Previous studies identified hyperleukocytosis, CNS involvement, and a younger or older age

as risk factors for ED.<sup>3-5</sup> Low performance status at diagnosis has also been associated with higher probabilities of ED,<sup>5</sup> but information on performance status was unavailable in our study. We were not able to confirm any of the above as significant risk factors, possibly due to a lack of statistical power, or maybe because of improved supportive care effects. We hypothesize that more knowledge on the risks of hyperleukocytosis, and early anticipation in combination with improved associated supportive care measures, like rasburicase, and a fast start of treatment has led to better outcome for patients with hyperleukocytosis.

The most important cause of TRM was infection. This is in line with reports from other study groups.<sup>4-6,15</sup> Infections mainly involved bacterial species, but two patients died in CR1, respectively, from Candida and Aspergillus infections. Younger age is a known risk factor for TRM.<sup>4,15</sup> Although the etiology remains unclear, infants are at known risk for toxicity and inappropriate dosing.<sup>16</sup>



**FIGURE 2** Cumulative incidence of treatment-related mortality in first complete remission  
 \* Other deaths include early death, death after refractory disease, and death after relapse  
 Abbreviations: CR1, first complete remission; TRM, treatment-related mortality

Immaturity of the immune system probably also contributes to high infection risks. CNS involvement was no risk factor in our study, but we defined CNS involvement as either CNS2 or CNS3, because older protocols did not distinguish between these two. Although both might be relevant, impact may be different and dependent on associated CNS treatment in relation to TRM. Therefore, future studies should focus not only on CNS status being either 2 or 3, but also on the intensity of CNS directed therapy, and preferably even the known association between several favorable cytogenetic/molecular aberrations and CNS involvement.<sup>17,18</sup> Lastly, overweight and underweight have both been associated with higher risk on severe toxicity and TRM.<sup>19–21</sup> Malnutrition is associated with lower socioeconomic status, a delay in diagnosis, and advanced disease.<sup>19,22</sup> Lange et al.<sup>19</sup> hypothesized that malnutrition reduces absorption, decreases drug-protein binding, and impedes oxidative and other metabolic reactions, resulting in lower efficacy and augmenting toxicity. However, specific pharmacological studies clarifying underlying mechanisms in pediatric AML patients are lacking. In our study, severe underweight was associated with more frequent ED. However, this should be interpreted with caution because of the limited number of patients. As a result of our small patient numbers, we were not able to perform multivariable analyses to study severe underweight as a potential independent risk factor for ED. Most patients with (severe) underweight were treated according to ANLL97. We hypothesize that the increasing body weight and BMI standards in the Dutch population over the past years explains this difference, although it could have been by chance as well. The most frequently reported cause of death among patients with (severe) underweight was refractory or ongoing disease (data not shown). Unfortunately, we were insufficiently informed on the BMI status of the patients throughout the treatment to study associations between weight in time and TRM. The effect of nutritional status on prognosis in pediatric AML is probably more complex and involves many

more aspects than BMI alone,<sup>23</sup> but other markers were lacking in our study.

Although beyond the scope of this article, we hypothesize that improved supportive care regimen over time contributed to lower ED rates and TRM over the past decades, with better transfusion regimens (e.g., irradiated products), more effective systemic infection prophylaxis plus better antibacterial and antifungal treatment, pursuing a better nutritional status (e.g., the use of nasogastric tube feeding and parenteral nutrition) and less tumor lysis-associated problems as most important contributors. Others have reported lower SCT-related TRM as a major contributor to improved OS,<sup>12</sup> but the number of patients who received allo-SCT in CR1 was probably too low to carry statistical impact on OS in our cohort; also, follow-up time was relatively short in this respect.

Our study has several limitations, mainly as a result of the retrospective design and the limited number of patients and events. There was a small overrepresentation of patients treated according to ANLL97 as a result of the relatively long inclusion time in that protocol. CR was defined based on morphology in all protocols as the earliest protocols did not include minimal residual disease (MRD) as response measurements. (flow-)MRD has been proven to be predictive for relapse risk and subsequent outcome by many study groups.<sup>24–28</sup> Future pediatric studies should include MRD-based early response assessment in defining CR and subsequent death in CR. Causes of death were extracted from the medical records. However, only in a few cases, causes of death were confirmed by an autopsy. In general, the most likely cause of death written down by the treating physician was adopted, but sometimes only symptomatic descriptions were registered in the chart. Causes of death according to the international classification of diseases (ICD-10) were not available, but it is likely that many patients who died from toxicity just have been registered as ICD-10 C92<sup>29</sup> (i.e., myeloid leukemia).



**TABLE 3** Causes of early death and death in first complete remission

Patient	Age at diagnosis (y)	Sex	Death	Protocol	Time of death	Cause of death
1	Unk	Unk	DBT	ANLL97	Before treatment	Unknown
2	Unk	Unk	DBT	ANLL97	Before treatment	Unknown
3	Unk	Unk	DBT	ANLL97	Before treatment	Unknown
4	2.3	M	ED	ANLL97	During treatment	Brain herniation due to leukostasis and infarction
5	14.5	M	ED	ANLL97	During treatment	Respiratory and circulatory insufficiency with multiorgan failure, CoNS infection
6	15.7	M	ED	ANLL97	During treatment	ARDS, sepsis (bacterial)
7	14.8	M	ED	ANLL97	During treatment	Candida sepsis, multiorgan failure
8	14.1	M	ED	ANLL97	During treatment	Ongoing disease (refused further treatment)
9	0.8	F	In CR1	ANLL97	During treatment	Septic shock
10	15.4	M	ED	ANLL97	During treatment	Septic shock
11	1.67	M	In CR1	ANLL97	During SCT trajectory	Complications after allo-SCT (pneumonia)
12	12.0	F	In CR1	ANLL97	During treatment	Pulmonary bleeding, aspergillosis
13	1.6	F	In CR1	ANLL97	After initial treatment	Cardiotoxicity; dilating cardiomyopathy
14	Unk	Unk	DBT	AML15	Before treatment	Unknown
15	Unk	Unk	DBT	AML15	Before treatment	Unknown
16	Unk	Unk	DBT	AML15	Before treatment	Unknown
17	4.5	F	ED	AML15	During treatment	Typhlitis, bacterial sepsis with cardiomyopathy, acute tubulus necrosis, ongoing disease
18	0.1	M	ED	AML15	During treatment	Respiratory insufficiency (not specified)
19	0.7	M	ED	AML15	During treatment	Cerebral hemorrhage, impingement
20	0.3	F	ED	AML15	During treatment	Ongoing disease, pericardial fluid, respiratory insufficiency
21	0.2	M	In CR1	AML15	During treatment	Meningitis (enterovirus), neurotoxicity, respiratory insufficiency
22	Unk	Unk	DBT	DB01	Before treatment	Unknown
23	<0.1	M	In CR1	DB01	During treatment	Candida sepsis, veno-occlusive disease, multiorgan failure
24	16.8	F	In CR1	DB01	During SCT trajectory	Complications after allo-SCT
25	13.2	M	ED	DB01	During treatment	Sepsis, respiratory insufficiency
26	2.6	M	ED	DB01	During treatment	Unknown/not specified

Abbreviations: ARDS, acute respiratory distress syndrome; CoNS, coagulase-negative staphylococci; CR1, first complete remission; DBT, death before treatment; ED, early death; F, female; M, male; (allo-)SCT, (allogenic) stem cell transplantation; unk, unknown; y, year.

As written IC was not available for patients who died prior to the onset of treatment, these patients could not be included in the analyses to identify risk factors for ED. Nonetheless, we collected registered deaths at time of the applicable protocols using the DCOG database, which did enable us to report the total number of ED more reliably.

Although we included a relatively large cohort of Dutch pediatric AML patients, the limited number of patients with an event hampered multivariable analyses and subsequent evaluation of independent risk factors for ED or TRM. A reliable evaluation of the potential impact of cytogenetic subgroups and molecular aberrations on probabilities of ED or TRM was not possible due to missing data from patients treated in the older protocols. Differences in supportive care or adaptations in treatment regimens were not taken into account. With the exception of allo-SCT, patients were evaluated according to the intention-to-treat

principle—in line with previous reports on this matter—but treatment adaptations based on toxicity, as well as intensified supportive care, may play an important role in probabilities of death in CR1. Lastly, the evaluation of allo-SCT-related mortality following relapse was beyond the scope of our study. Although the antileukemic effect of allo-SCT has been established in multiple studies, lower relapse rates need to be balanced against SCT-related mortality and morbidity.<sup>30–33</sup> Our study was not designed to evaluate overall SCT-related mortality.

## 5 | CONCLUSIONS

In conclusion, we report relatively stable rates of ED and TRM in CR1 in the latest completed DCOG protocols for newly diagnosed AML. The most important causes of TRM were infectious- and

SCT-related complications. These findings are relevant for designing new treatment protocols and supportive care guidelines. Future trials should focus on identifying novel risk factors, as well as on how to maintain or preferably further improve these numbers, at the same time warranting effectiveness. In this, nutritional support and infection control are probably key issues.

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## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

## CONFLICTS OF INTEREST

The authors report no relevant conflicts of interest.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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