Leukemia (2016) **30,** 24–31

www.nature.com/leu

ORIGINAL ARTICLE

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

AG Dinmohamed[1,6], O Visser[2,6], Y van Norden[3], NMA Blijlevens[4], JJ Cornelissen[1], GA Huls[4], PC Huijgens[2,5], P Sonneveld[1], AA van de Loosdrecht[5], GJ Ossenkoppele[5], B Löwenberg[1] and M Jongen-Lavrencic[1]

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 years. 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 years) 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.

Leukemia (2016) **30,** 24–31; doi:10.1038/leu.2015.188

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 pretreatment (for example, patient- and disease-related characteristics) and post-treatment factors (for example, 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 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 (SCT) 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 40–50% 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 (for example, 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 nonstudied population. Population-based studies can complement clinical trial studies and lend additional data informing clinical decision making.[27] Furthermore, nationwide population-based studies that

[1]Department of Hematology, Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, The Netherlands; [2]Netherlands Comprehensive Cancer Organisation, Utrecht, The Netherlands; [3]Clinical Trial Center-HOVON Data Center, Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, The Netherlands; [4]Department of Hematology, Radboud University Medical Center, Nijmegen, The Netherlands and [5]Department of Hematology, VU University Medical Center, Cancer Center Amsterdam, Amsterdam, The Netherlands. Correspondence: Dr M Jongen-Lavrencic, Department of Hematology, Erasmus MC Cancer Institute, Erasmus University Medical Center, Wytemaweg 80, Rotterdam 3015 CN, ZH, The Netherlands.
E-mail: m.lavrencic@erasmusmc.nl
[6]These authors contributed equally to this work.
Received 13 May 2015; revised 29 June 2015; accepted 8 July 2015; accepted article preview online 17 July 2015; advance online publication, 7 August 2015

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 >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.

PATIENTS AND METHODS

Registry and study population

The NCR, which is maintained and hosted by the Netherlands Comprehensive Cancer Organisation, has an overall coverage of >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 and 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[(ref. 32)] in 2001, myelodysplastic syndromes and myeloproliferative neoplasms were considered nonmalignant hematologic diseases. Therefore, the progression from myelodysplastic syndromes or myeloproliferative neoplasms to AML was included in the NCR as a first incident case of AML before 2001, whereas as of 2001, myelodysplastic syndromes and myeloproliferative neoplasms 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 (1 February 2014), whichever occurred first.

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

Disease type	*Characteristics*	*Calendar period*								*Total*	
		1989–1994		*1995–2000*		*2001–2006*		*2007–2012*			
		No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
AML	Total No. of patients	2599		2983		3365		3668		12 615	
	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: AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; ASR, age-standardized incidence rate. [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.

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 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

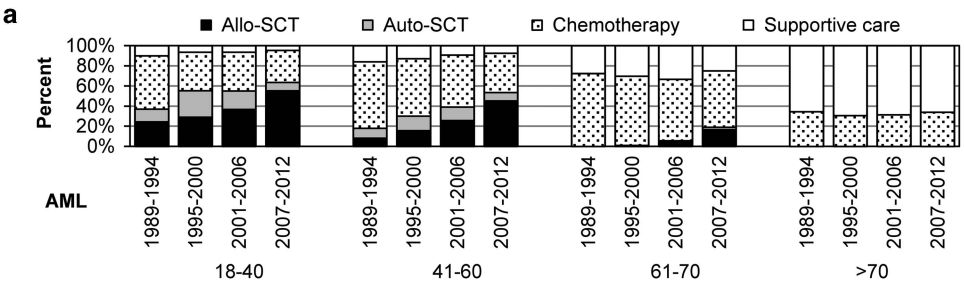
Relative survival rates (RSRs) with 95% confidence intervals (CIs) were calculated as a measure of disease-specific survival according to the cohort methodology. Relative survival is the ratio of the observed survival of patients to the expected survival of a comparable cohort from the general population, 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 <0.20 in univariate analysis were included in the multivariate analysis. A *P*-value <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, USA).

RESULTS

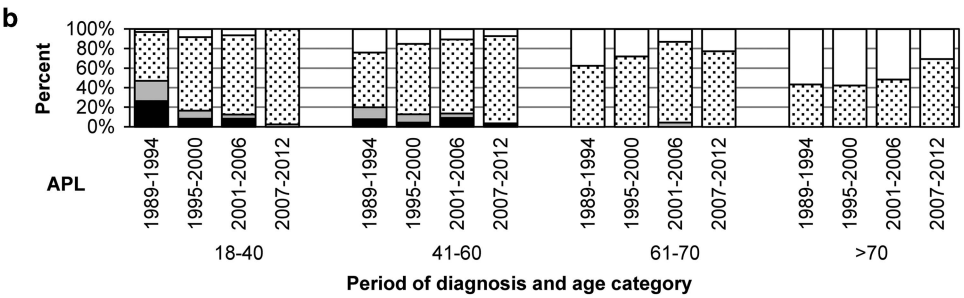
Demographic characteristics

A total of 12 615 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 owing to the revised blast threshold for the diagnosis of AML from 30 to



Treatment	Column percentage															
Supportive care	10%	7%	6%	5%	16%	13%	9%	8%	28%	30%	33%	25%	65%	69%	69%	66%
Chemotherapy	53%	38%	39%	32%	66%	57%	52%	39%	72%	69%	61%	56%	35%	31%	31%	34%
Auto-SCT	13%	27%	19%	8%	10%	15%	13%	8%	0%	1%	0%	2%	-	-	-	-
Allo-SCT	24%	29%	37%	55%	8%	16%	26%	46%	-	0%	6%	17%	-	-	0%	0%



Treatment	Column percentage															
Supportive care	3%	8%	6%	-	24%	15%	11%	7%	38%	28%	13%	23%	57%	58%	52%	31%
Chemotherapy	50%	75%	81%	97%	56%	72%	75%	89%	63%	72%	83%	77%	43%	42%	48%	69%
Auto-SCT	21%	8%	4%	3%	12%	9%	5%	1%	-	-	4%	-	-	-	-	-
Allo-SCT	26%	8%	9%	-	8%	4%	9%	2%	-	-	-	-	-	-	-	-

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.

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 Figures 1a and b, respectively. The application of allo-SCT for AML increased over time among patients <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 ~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

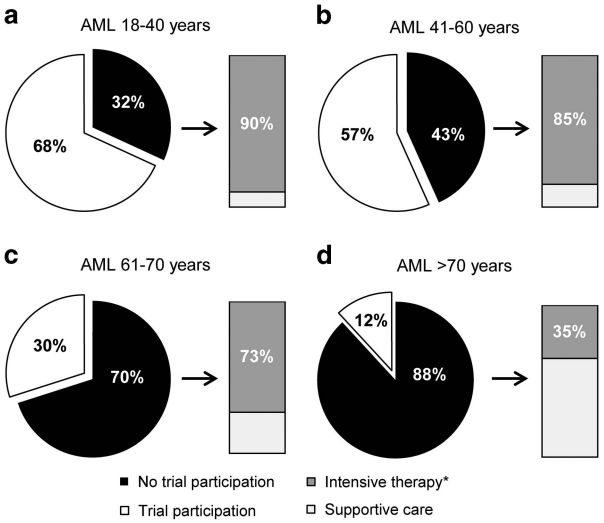
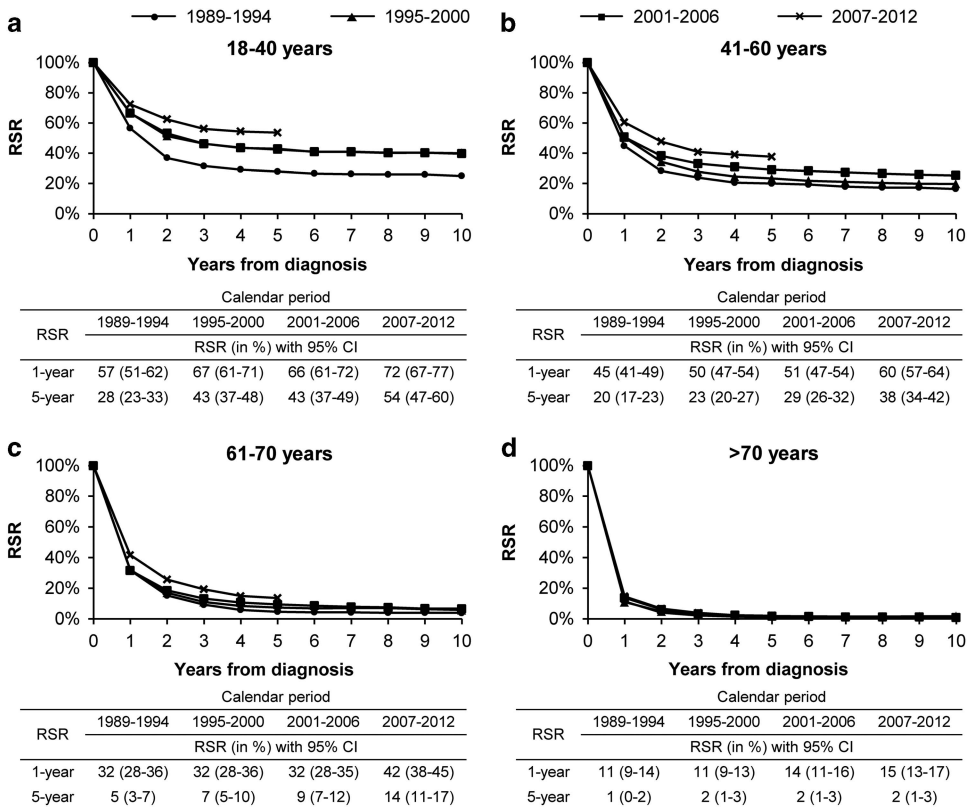


Figure 2. Trial participation of adult patients with AML in the Netherlands according to age at diagnosis. The pie chart depicts the proportion of trial participation among patients aged (**a**) 18–40 years, (**b**) 41–60 years, (**c**) 61–70 years and (**d**) >70 years. The bar plot depicts the treatment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



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.

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).

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. 90%, 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.

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–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, that is, 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.

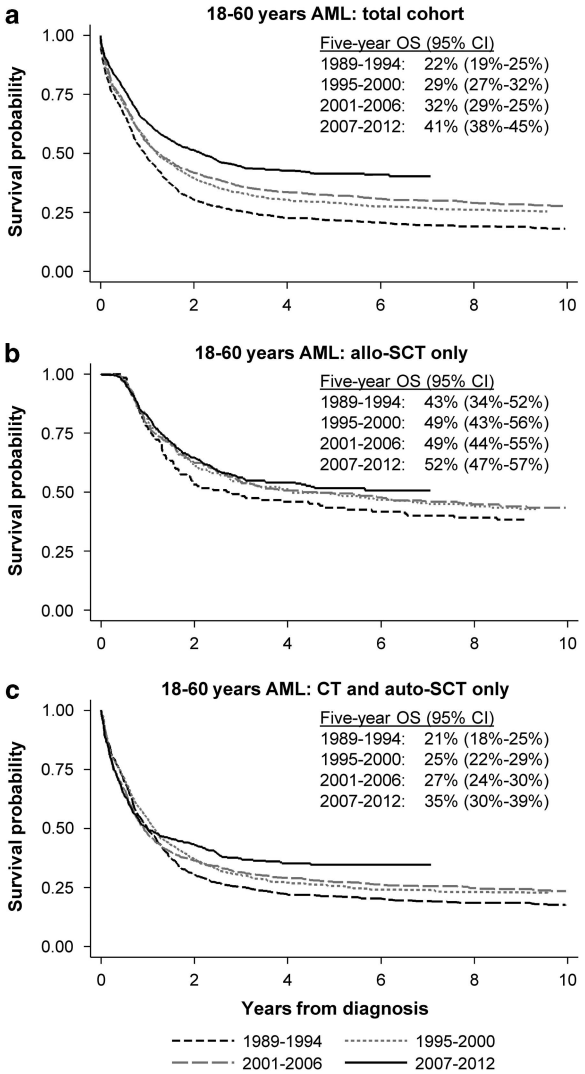
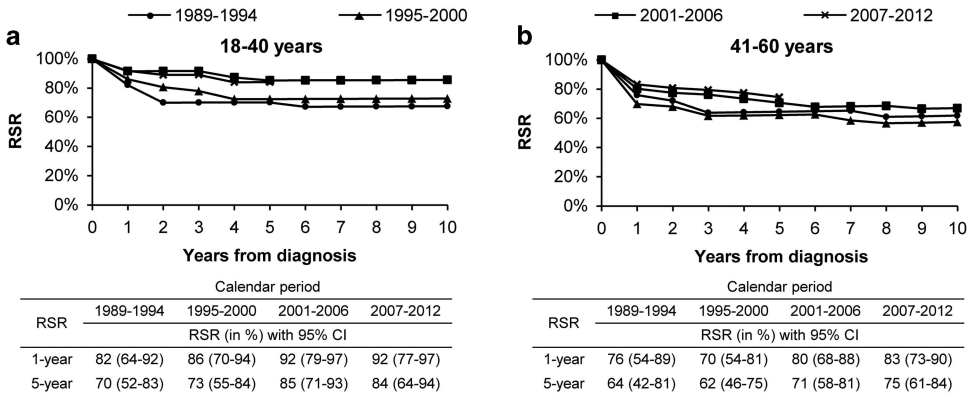


Figure 4. Overall survival (OS) of patients with AML 18–60 years of age according to treatment and calendar period of diagnosis, 1989–2012. Kaplan–Meier estimates of OS according to (**a**) all treatment choices (that is, supportive care only, chemotherapy, allo-SCT and auto-SCT), (**b**) allo-SCT and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

DISCUSSION

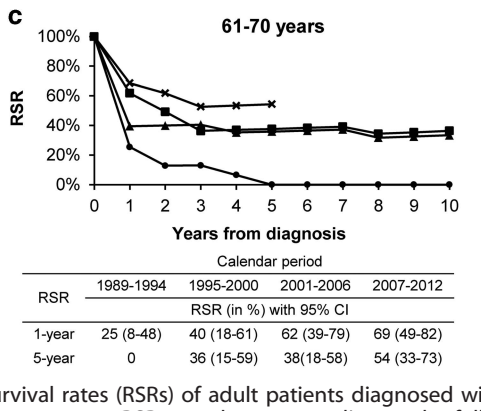
Most published population-based cancer registry studies in AML provide information on survival at the population level,[2,3,21,35–37] whereas only a few assessed the application of various treatments.[22,38,39] Further, long-term data are lacking on trial participation in an unselected AML population. 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] that is, a lower incidence and a higher median age at diagnosis compared with other population-based reports,[3,41–43] and gender differences

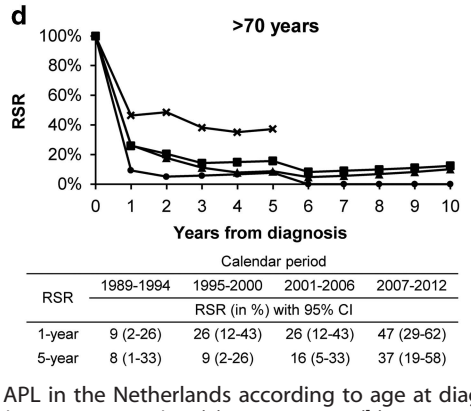


RSR	Calendar period			
	1989-1994	1995-2000	2001-2006	2007-2012
	RSR (in %) with 95% CI			
1-year	82 (64-92)	86 (70-94)	92 (79-97)	92 (77-97)
5-year	70 (52-83)	73 (55-84)	85 (71-93)	84 (64-94)

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.

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 with 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 with 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] Second, 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 nonrelapse 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 noninclusion were: advanced age; comorbidities and an antecedent malignancy, including a hematologic malignancy (for example, 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 all-*trans* retinoic acid in the mid-1980 s 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 all-*trans* retinoic acid 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 all-*trans* retinoic acid 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 (for example, comorbidity and performance status) and disease-related characteristics (for example, 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.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

We thank the Dutch-Belgian Cooperative Trial Group for Hemato-Oncology (HOVON) and the European Organization for Research and Treatment of Cancer (EORTC) for permission to use data on trial participation from their clinical AML trials for this research. We also thank the Stem Cell Transplantation (SCT) Working Party of the HOVON for permission to use data on SCTs for this study. We are grateful to Dr Mirian Brink (Netherlands Comprehensive Cancer Organisation) for additional data analysis. The contents of this publication and methods used are solely the responsibility of the authors and do not necessarily represent the official views of the EORTC. This work was supported by a grant from The Netherlands Organization for Health Research and Development (ZonMw; grant #152001007).

AUTHOR CONTRIBUTIONS

AGD, OV and MJ-L designed the study; OV analyzed the data; OV, YvN and JJC collected the data; AGD wrote the manuscript with contributions from OV, YvN, NMNA, JJC, GAH, PCH, PS, AAvdL, GJO, BL and MJ-L; and all authors read, commented on and approved the final version of the manuscript.

REFERENCES

1 Estey E, Dohner H. Acute myeloid leukaemia. *Lancet* 2006; **368**: 1894–1907.
2 Visser O, Trama A, Maynadie M, Stiller C, Marcos-Gragera R, De Angelis R *et al.* Incidence, survival and prevalence of myeloid malignancies in Europe. *Eur J Cancer* 2012; **48**: 3257–3266.
3 Dores GM, Devesa SS, Curtis RE, Linet MS, Morton LM. Acute leukemia incidence and patient survival among children and adults in the United States, 2001–2007. *Blood* 2012; **119**: 34–43.
4 Ostgard LS, Norgaard JM, Sengelov H, Holm MS, Jensen MK, Kallenbach M *et al.* Impact of chemotherapy delay on short- and long-term survival in younger and older AML patients: a Danish population-based cohort study. *Leukemia* 2014; **28**: 1926–1929.
5 Dohner H, Estey EH, Amadori S, Appelbaum FR, Buchner T, Burnett AK *et al.* Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. *Blood* 2010; **115**: 453–474.
6 Ossenkoppele G, Lowenberg B. How I treat the older patient with acute myeloid leukemia. *Blood* 2015; **125**: 767–774.
7 Burnett A, Wetzler M, Lowenberg B. Therapeutic advances in acute myeloid leukemia. *J Clin Oncol* 2011; **29**: 487–494.
8 Wang ZY, Chen Z. Acute promyelocytic leukemia: from highly fatal to highly curable. *Blood* 2008; **111**: 2505–2515.
9 Sanz MA, Grimwade D, Tallman MS, Lowenberg B, Fenaux P, Estey EH *et al.* Management of acute promyelocytic leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. *Blood* 2009; **113**: 1875–1891.
10 Gafter-Gvili A, Fraser A, Paul M, Leibovici L. Meta-analysis: antibiotic prophylaxis reduces mortality in neutropenic patients. *Ann Intern Med* 2005; **142**: 979–995.
11 Horan JT, Logan BR, Agovi-Johnson MA, Lazarus HM, Bacigalupo AA, Ballen KK *et al.* Reducing the risk for transplantation-related mortality after allogeneic hematopoietic cell transplantation: how much progress has been made? *J Clin Oncol* 2011; **29**: 805–813.
12 Lowenberg B, Ossenkoppele GJ, van Putten W, Schouten HC, Graux C, Ferrant A *et al.* High-dose daunorubicin in older patients with acute myeloid leukemia. *N Engl J Med* 2009; **361**: 1235–1248.
13 Lowenberg B, Pabst T, Vellenga E, van Putten W, Schouten HC, Graux C *et al.* Cytarabine dose for acute myeloid leukemia. *N Engl J Med* 2011; **364**: 1027–1036.
14 Copelan EA. Hematopoietic stem-cell transplantation. *N Engl J Med* 2006; **354**: 1813–1826.
15 Schlenk RF, Dohner H. Genomic applications in the clinic: use in treatment paradigm of acute myeloid leukemia. *Hematology Am Soc Hematol Educ Program* 2013; **2013**: 324–330.
16 Cornelissen JJ, van Putten WL, Verdonck LF, Theobald M, Jacky E, Daenen SM *et al.* Results of a HOVON/SAKK donor versus no-donor analysis of myeloablative HLA-identical sibling stem cell transplantation in first remission acute myeloid leukemia in young and middle-aged adults: benefits for whom? *Blood* 2007; **109**: 3658–3666.
17 Burnett AK, Russell NH, Hills RK, Hunter AE, Kjeldsen L, Yin J *et al.* Optimization of chemotherapy for younger patients with acute myeloid leukemia: results of the medical research council AML15 trial. *J Clin Oncol* 2013; **31**: 3360–3368.
18 Willemze R, Suciu S, Meloni G, Labar B, Marie JP, Halkes CJ *et al.* High-dose cytarabine in induction treatment improves the outcome of adult patients younger than age 46 years with acute myeloid leukemia: results of the EORTC-GIMEMA AML-12 trial. *J Clin Oncol* 2014; **32**: 219–228.
19 Goldstone AH, Burnett AK, Wheatley K, Smith AG, Hutchinson RM, Clark RE *et al.* Attempts to improve treatment outcomes in acute myeloid leukemia (AML) in older patients: the results of the United Kingdom Medical Research Council AML11 trial. *Blood* 2001; **98**: 1302–1311.
20 Buchner T, Berdel WE, Haferlach C, Haferlach T, Schnittger S, Muller-Tidow C *et al.* Age-related risk profile and chemotherapy dose response in acute myeloid leukemia: a study by the German Acute Myeloid Leukemia Cooperative Group. *J Clin Oncol* 2009; **27**: 61–69.
21 Derolf AR, Kristinsson SY, Andersson TM, Landgren O, Dickman PW, Bjorkholm M. Improved patient survival for acute myeloid leukemia: a population-based study of 9729 patients diagnosed in Sweden between 1973 and 2005. *Blood* 2009; **113**: 3666–3672.
22 Juliusson G, Antunovic P, Derolf A, Lehmann S, Mollgard L, Stockelberg D *et al.* Age and acute myeloid leukemia: real world data on decision to treat and outcomes from the Swedish Acute Leukemia Registry. *Blood* 2009; **113**: 4179–4187.
23 Mengis C, Aebi S, Tobler A, Dahler W, Fey MF. Assessment of differences in patient populations selected for excluded from participation in clinical phase III acute myelogenous leukemia trials. *J Clin Oncol* 2003; **21**: 3933–3939.
24 Stevens JM, Macdougall F, Jenner M, Oakervee H, Cavenagh J, Lister AT. Patterns of recruitment into acute myeloid leukaemia (AML) 15 and outcome for young patients with AML at a single referral centre. *Br J Haematol* 2009; **145**: 40–44.
25 Dechartres A, Chevret S, Lambert J, Calvo F, Levy V. Inclusion of patients with acute leukemia in clinical trials: a prospective multicenter survey of 1066 cases. *Ann Oncol* 2011; **22**: 224–233.
26 Lazarevic V, Horstedt AS, Johansson B, Antunovic P, Billstrom R, Derolf A *et al.* Incidence and prognostic significance of karyotypic subgroups in older patients with acute myeloid leukemia: the Swedish population-based experience. *Blood Cancer J* 2014; **4**: e188.
27 Juliusson G, Lazarevic V, Horstedt AS, Hagberg O, Hoglund M. Swedish Acute Leukemia Registry Group. Acute myeloid leukemia in the real world: why population-based registries are needed. *Blood* 2012; **119**: 3890–3899.
28 Schouten LJ, Hoppener P, van den Brandt PA, Knottnerus JA, Jager JJ. Completeness of cancer registration in Limburg, The Netherlands. *Int J Epidemiol* 1993; **22**: 369–376.
29 Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR *et al.* Proposed revised criteria for the classification of acute myeloid leukemia. A report of the French-American-British Cooperative Group. *Ann Intern Med* 1985; **103**: 620–625.
30 Jaffe ES, Harris NL, Stein H, Vardiman JW. (eds). *Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues*. IARC: Lyon, 2001.
31 Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H *et al.* (eds). *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. IARC: Lyon, 2008.

32 Fritz AG, Percy C, Jack A, Sobin LH, Parkin DM. (eds). *International Classification of Diseases for Oncology*, 3rd edn. World Health Organization: Geneva, 2000.
33 Dickman PW, Adami HO. Interpreting trends in cancer patient survival. *J Intern Med* 2006; **260**: 103–117.
34 Hakulinen T. Cancer survival corrected for heterogeneity in patient withdrawal. *Biometrics* 1982; **38**: 933–942.
35 Pulte D, Gondos A, Brenner H. Improvements in survival of adults diagnosed with acute myeloblastic leukemia in the early 21st century. *Haematologica* 2008; **93**: 594–600.
36 Thein MS, Ershler WB, Jemal A, Yates JW, Baer MR. Outcome of older patients with acute myeloid leukemia: an analysis of SEER data over 3 decades. *Cancer* 2013; **119**: 2720–2727.
37 Sant M, Minicozzi P, Mounier M, Anderson LA, Brenner H, Holleczek B *et al.* Survival for haematological malignancies in Europe between 1997 and 2008 by region and age: results of EUROCARE-5, a population-based study. *Lancet Oncol* 2014; **15**: 931–942.
38 Lang K, Earle CC, Foster T, Dixon D, Van Gool R, Menzin J. Trends in the treatment of acute myeloid leukaemia in the elderly. *Drugs Aging* 2005; **22**: 943–955.
39 Oran B, Weisdorf DJ. Survival for older patients with acute myeloid leukemia: a population-based study. *Haematologica* 2012; **97**: 1916–1924.
40 Lehmann S, Ravn A, Carlsson L, Antunovic P, Deneberg S, Mollgard L *et al.* Continuing high early death rate in acute promyelocytic leukemia: a population-based report from the Swedish Adult Acute Leukemia Registry. *Leukemia* 2011; **25**: 1128–1134.
41 Tomas JF, Fernandez-Ranada JM. About the increased frequency of acute promyelocytic leukemia among Latinos: the experience from a center in Spain. *Blood* 1996; **88**: 2357–2358.
42 Douer D, Preston-Martin S, Chang E, Nichols PW, Watkins KJ, Levine AM. High frequency of acute promyelocytic leukemia among Latinos with acute myeloid leukemia. *Blood* 1996; **87**: 308–313.
43 Park JH, Qiao B, Panageas KS, Schymura MJ, Jurcic JG, Rosenblat TL *et al.* Early death rate in acute promyelocytic leukemia remains high despite all-trans retinoic acid. *Blood* 2011; **118**: 1248–1254.
44 Juliusson G, Karlsson K, Lazarevic V, Wahlin A, Brune M, Antunovic P *et al.* Hematopoietic stem cell transplantation rates and long-term survival in acute myeloid and lymphoblastic leukemia: real-world population-based data from the Swedish Acute Leukemia Registry 1997-2006. *Cancer* 2011; **117**: 4238–4246.
45 Hahn T, McCarthy Jr PL, Hassebroek A, Bredeson C, Gajewski JL, Hale GA *et al.* Significant improvement in survival after allogeneic hematopoietic cell transplantation during a period of significantly increased use, older recipient age, and use of unrelated donors. *J Clin Oncol* 2013; **31**: 2437–2449.
46 Passweg JR, Baldomero H, Bader P, Bonini C, Cesaro S, Dreger P *et al.* Hematopoietic SCT in Europe 2013: recent trends in the use of alternative donors showing more haploidentical donors but fewer cord blood transplants. *Bone Marrow Transplant* 2015; **50**: 476–482.
47 Slovak ML, Kopecky KJ, Cassileth PA, Harrington DH, Theil KS, Mohamed A *et al.* Karyotypic analysis predicts outcome of preremission and postremission therapy in adult acute myeloid leukemia: a Southwest Oncology Group/Eastern Cooperative Oncology Group Study. *Blood* 2000; **96**: 4075–4083.
48 Koreth J, Schlenk R, Kopecky KJ, Honda S, Sierra J, Djulbegovic BJ *et al.* Allogeneic stem cell transplantation for acute myeloid leukemia in first complete remission: systematic review and meta-analysis of prospective clinical trials. *JAMA* 2009; **301**: 2349–2361.
49 Gale RP, Wiernik PH, Lazarus HM. Should persons with acute myeloid leukemia have a transplant in first remission? *Leukemia* 2014; **28**: 1949–1952.
50 Schlenk RF, Dohner K, Mack S, Stoppel M, Kiraly F, Gotze K *et al.* Prospective evaluation of allogeneic hematopoietic stem-cell transplantation from matched related and matched unrelated donors in younger adults with high-risk acute myeloid leukemia: German-Austrian trial AMLHD98A. *J Clin Oncol* 2010; **28**: 4642–4648.
51 Cornelissen JJ, Gratwohl A, Schlenk RF, Sierra J, Bornhauser M, Juliusson G *et al.* The European LeukemiaNet AML Working Party consensus statement on allogeneic HSCT for patients with AML in remission: an integrated-risk adapted approach. *Nat Rev Clin Oncol* 2012; **9**: 579–590.
52 Giles FJ, Borthakur G, Ravandi F, Faderl S, Verstovsek S, Thomas D *et al.* The haematopoietic cell transplantation comorbidity index score is predictive of early death and survival in patients over 60 years of age receiving induction therapy for acute myeloid leukaemia. *Br J Haematol* 2007; **136**: 624–627.
53 Klepin HD, Geiger AM, Tooze JA, Kritchevsky SB, Williamson JD, Pardee TS *et al.* Geriatric assessment predicts survival for older adults receiving induction chemotherapy for acute myelogenous leukemia. *Blood* 2013; **121**: 4287–4294.
54 Fenaux P, Mufti GJ, Hellstrom-Lindberg E, Santini V, Gattermann N, Germing U *et al.* Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. *J Clin Oncol* 2010; **28**: 562–569.
55 Dombret H, Seymour JF, Butrym A, Wierzbowska A, Selleslag D, Jang JH *et al.* International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with $>30\%$ blasts. *Blood* 2015; **126**: 291–299.
56 Kantarjian HM, Thomas XG, Dmoszynska A, Wierzbowska A, Mazur G, Mayer J *et al.* Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. *J Clin Oncol* 2012; **30**: 2670–2677.
57 Scher KS, Hurria A. Under-representation of older adults in cancer registration trials: known problem, little progress. *J Clin Oncol* 2012; **30**: 2036–2038.
58 Dinmohamed AG, van Norden Y, Visser O, Posthuma EF, Huijgens PC, Sonneveld P *et al.* The use of medical claims to assess incidence, diagnostic procedures and initial treatment of myelodysplastic syndromes and chronic myelomonocytic leukemia in the Netherlands. *Leukemia research* 2015; **39**: 177–182.
59 Fenaux P, Chastang C, Chevret S, Sanz M, Dombret H, Archimbaud E *et al.* A randomized comparison of all transretinoic acid (ATRA) followed by chemotherapy and ATRA plus chemotherapy and the role of maintenance therapy in newly diagnosed acute promyelocytic leukemia. The European APL Group. *Blood* 1999; **94**: 1192–1200.
60 Tallman MS, Andersen JW, Schiffer CA, Appelbaum FR, Feusner JH, Ogden A *et al.* All-trans-retinoic acid in acute promyelocytic leukemia. *N Engl J Med* 1997; **337**: 1021–1028.

Supplementary Information accompanies this paper on the Leukemia website (http://www.nature.com/leu)