Improvements in survival of adults diagnosed with acute myeloblastic leukemia in the early 21st century

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ABSTRACT

Treatment of adults with acute myeloblastic leukemia has changed substantially over the past two decades. Currently available estimates of survival do not reflect results from present state-of-the-art treatment due to a lag between the availability of new treatments and data concerning their effect on survival on the population level when traditional cohort analysis is used. We estimated trends in age-specific 5- and 10-year relative survival of acute myeloblastic leukemia patients aged over 15 years old for 5-year calendar periods from 1980-1984 through 2000-2004 using data from the Surveillance, Epidemiology, and End Results Program. Period analysis was employed to reveal recent developments in prognosis. Five and 10-year relative survival improved greathy between 1980-1984 and 2000-2004 for all patients except those aged over 75 years old. Improvements were greatest for patients aged 15-34, with increases in 5- and 10-year relative survival of greater than 30% points in this group. Five and 10-year relative survival reached 52.3% and 47.9%, respectively, in this group in 2000-2004. Less pronounced but still substantial improvements in relative survival were seen in the 35-54 and 55-64 age groups. Survival was unchanged, at less than 5%, for patients aged over 75 years old. Our period analysis reveals major improvement on the population level in long-term prognosis of younger patients with acute myeloblastic leukemia, most likely explained by multiple incremental improvements in care including better and more specific diagnosis, improvements in and extension of the use of stem cell transplantation and high dose therapy, and improved supportive care.

Key words: period analysis, acute myeloblastic leukemia, prognosis

Citation: Pulte D, Gondos A and Brenner H. Improvements in survival of adults diagnosed with acute myeloblastic leukemia in the early 21st century. Haematologica 2008 Apr; 93(4):594-600. doi: 10.3324/haematol.12304

Introduction

Treatment of acute myeloblastic leukemia (AML) has evolved greatly over the past several decades, with improvements in allogenic and autologous hematopoietic stem cell transplantation and supportive care,[1] as well as the introduction of new treatments such as all-trans retinoic acid (ATRA),[2,3] and the use of high-dose cytarabine as consolidation therapy,[4] which have enhanced the outlook for patients with AML over the past decade. Existing estimates of long-term survival of patients with AML from population-based cancer registries reflect the prognosis of patients diagnosed up to the early and mid 1990s, and thus do not capture the potential impact of recent advances in therapy. Additionally, although improvements in survival for patients with AML after several specific therapeutic interventions have been observed in clinical trials, the impact of these interventions at the population level has not been examined in detail. Patients in clinical trials tend to be highly selected and may have better survival than patients in the general population.[5] In particular, older patients and patients from racial minorities, both of whom tend to have worse outcomes, are generally underrepresented in clinical trials.[6,7] The results of clinical trials may, therefore, not reflect the survival expectations of the "average" patient. We aimed to determine recent trends in and up-to-date estimates of long-term survival of AML patients by the technique of period survival analysis.[8,9] Due to the differential application of novel therapies according to age, we were specifically interested in age-specific trends in prognosis.

Methods

All data presented in this paper are derived from the 1973-2004 limited-use database of the Surveillance, Epidemiology, and End Results (SEER) Program of the United States National Cancer Institute issued in April 2007.[10] Data included in the 1973-2004 SEER database are from population-based cancer registries in Connecticut, New Mexico, Utah, Iowa, Hawaii, Atlanta, Detroit, Seattle-Puget Sound and San Francisco-Oakland which together cover a population of

Funding: the work of Dr. Pulte was supported by a Visiting Faculty Research Grant from the German Academic Exchange Service (DAAD) and a Merit Review Grant from the Department of Veterans Affairs.
Manuscript received September 26, 2007. Revised version arrived on October 30, 2007. Manuscript accepted November 22, 2007.
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about 30 million people. Geographic areas were selected for inclusion in the SEER Program based on their ability to operate and maintain a high-quality population-based cancer reporting system and for their epidemiologically significant population subgroups. The SEER population is comparable to the general United States population with regards to measures of poverty and education, even though it tends to be somewhat more urban and has a higher proportion of foreign-born persons than the general population.

The database included 15,638 patients aged 15 years or older with a first diagnosis of AML (and no previous cancer diagnosis) between 1980 and 2004, who were followed for vital status until the end of 2004. After exclusion of 47 patients (0.3%) who were included in the database by autopsy results only and of 182 patients (1.2%) who were included by death certificate only, 15,409 patients (98.5%) remained for the survival analysis. Cases were selected using ICD-O-3 coding for AML. This coding was used because it is available for all time periods studied and therefore eliminates any bias that might occur due to different coding systems. We considered all types of AML as a single group because the numbers of patients in each subgroup of AML were inadequate for separate analyses. Patients with acute pro-myelocytic leukemias (APL) were included in the analysis. The percentage of patients with APL was essentially stable over time and accounted for approximately 5% of cases in each time period.

Five- and 10-year survival was calculated for the calendar periods 1980-1984, 1985-1989, 1990-1994, 1995-1999, and 2000-2004 using the period analysis methodology.[8] Furthermore, we tested trends in 5- and 10-year year survival between 1980-1984 and 2000-2004 for statistical significance using a recently described modeling approach.[11] All analyses were carried out separately for the following five major age groups: 15-34, 35-54, 55-64, 65-74, and over 75 year olds.

With period analysis, as first proposed by Brenner and Gefeller in 1996,[8] only survival experience during the period of interest is included in the analysis. This is achieved by left truncation of observations at the beginning of the period in addition to right censoring at its end. A graphical illustration of the data included to estimate 10-year relative survival for the 2000-2004 period compared to the data used to derive the most up-to-date estimate of 10-year survival from the same database using traditional cohort analysis is shown in Figure 1. The latter would pertain to patients diagnosed in 1990-1994 only and would thus not capture results from recent progress in therapy. It has been shown by extensive empirical evaluation that period analysis provides more up-to-date long-term survival estimates than traditional cohort-based survival analy-

Year of diagnosis	Year of follow-up														
	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
1990	1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10				
1991		1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10			
1992			1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10		
1993				1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10	
1994					1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10
1995						1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10
1996							1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9
1997								1	1-2	2-3	3-4	4-5	5-6	6-7	7-8
1998									1	1-2	2-3	3-4	4-5	5-6	6-7
1999										1	1-2	2-3	3-4	4-5	5-6
2000											1	1-2	2-3	3-4	4-5
2001												1	1-2	2-3	3-4
2002													1	1-2	2-3
2003														1	1-2
2004															1

Figure 1. Data used for estimating 10-year survival for the 2000-2004 period by period analysis (closed frame). For comparison, data used to derive the most up-to-date estimates of 10-year survival from the same database using traditional cohort analysis are shown (dashed frame).

Table 1. Numbers of patients with acute myeloblastic leukemia by age group and calendar period.

	Calendar period					
Age	1980-84	1985-89	1990-94	1995-99	2000-04	Total
All	2,573	2,683	2,987	3,419	3,747	15,409
15-34	299	290	316	335	398	1,638
35-54	450	481	542	699	691	2,863
55-64	429	453	437	482	565	2,366
65-74	615	658	797	803	817	3,690
75+	780	801	895	1,100	1,276	4,852

sis, and quite closely predicts long-term survival expectations of cancer patients diagnosed within the period of interest.[9,12]

According to standard practice in population-based cancer survival analysis, relative rather than absolute survivals were calculated. Relative survival reflects survival of cancer patients compared to survival of the general population. It is calculated as the ratio of absolute survival of cancer patients divided by the expected survival of a group of people of the corresponding sex, age and race in the general population.[13,14] Estimates of expected survival were derived according to the so-called Ederer II method[15] using US sex-, age-, and race-specific life tables.[16]

All analyses were performed with the SAS software package using adapted versions of previously described macros for period analysis.[11,17]

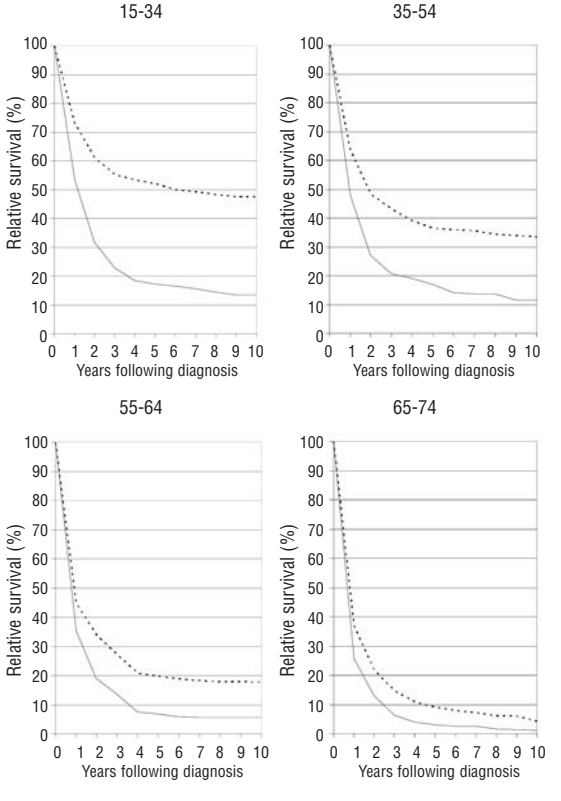

Figure 2. Ten-year relative survival curves of patients with AML by major age groups. Period estimates are for 1980-1984 (solid curves) and 2000-2004 (dashed curves).

Table 2. Five- and 10-year estimates of relative survival of patients with acute myeloblastic leukemia by age group and calendar period.

		Calendar period					
		1980-1984		2000-2004			
	Age	PE	SE	PE	SE	Increase[a]	p value[b]
5-year relative survival	All	8.4	0.6	19.5	0.7	11.1	<0.0001
	15-34	17.4	2.2	52.3	2.6	34.9	<0.0001
	35-54	16.9	1.9	36.6	1.9	19.7	<0.0001
	55-64	6.7	1.4	19.9	1.9	13.2	<0.0001
	65-74	3.0	0.9	9.2	1.3	6.2	<0.0001
	75+	3.8	1.1	2.5	0.7	-1.3	0.54
10-year relative survival	All	5.6	0.7	17.1	0.7	11.5	<0.0001
	15-34	13.5	2.2	47.9	2.7	34.4	<0.0001
	35-54	11.6	1.9	33.6	1.9	22.0	<0.0001
	55-64	5.6	1.4	17.9	2.0	12.3	<0.0001
	65-74	1.2	0.6	4.5	1.2	3.3	<0.0001
	75+	0.1	-	1.0	0.5	0.9	0.55

[a]*Increase from 1980-1984 to 2000-2004 in percentage points*
[b]*P value for trend from 1980-1984 to 2000-2004*
(PE: point estimate, SE: standard error)

Results

The numbers of cases for each time period and for each age category are shown in Table 1. The total number of cases increased between 1980-1984 and 2000-2004, rising from 2,573 to 3,747 cases. The over 75-year old age group was the largest and the group aged 15-34 years old the smallest for each calendar period. The largest individual category was patients aged 75 or older who were diagnosed in 2000-20004, with 1,276 cases; the smallest was patients aged 15-34 years old diagnosed in 1985-1989, with 290 cases.

Relative survival improved substantially for patients with AML between the years 1980-1984 and 2000-2004. Overall, 5- and 10-year survival rose from 8.4% and 5.6% to 19.5% and 17.1%, respectively. Highly significant improvements in survival were seen for all age groups except for patients aged 75 and over (Table 2). The largest individual gain was in patients aged 15-34, for whom the probability of surviving 10 years increased by more than 34% points, from 13.5% in 1980-1984 to 47.9% in 2000-2004 ($p<0.0001$). By contrast, 10-year relative survival remained close to zero and below 5% among patients aged over 75 years old and 65-74 years old, respectively, even in 2000-2004.

A more comprehensive presentation of survival according to time since diagnosis in the earliest (1980-1984) and most recent (2000-2004) periods is given in Figure 2. Ten-year relative survival curves show a general flattening by 4 to 5 years after diagnosis for

patients in the younger age groups in 2000-2004, indicating that few patients who survived 4-5 years died in the subsequent 5-6 years (Figure 2). Patients older than 65 had continued decreases in the relative survival rate for at least 10 years after diagnosis, although the rate of decrease slowed about 4 years after diagnosis. Survival curves for 1980-1984 showed much lower survival rates, with an especially steep drop in survival in the first 2-3 years after diagnosis for patients aged 15-34 years old and moderately worse survival for patients aged 35-54, 55-64, and 65-74.

A graphic representation of changes in the age-specific 5-year relative survival according to calendar period is shown in Figure 3. Survival improved steadily for patients aged 15-34 throughout the periods between 1980-1984 and 2000-2004. Survival improved less dramatically but fairly steadily for patients aged 35-54 during the same time periods, increasing from less than 15% to over 30%. Survival has improved gradually but consistently for patients aged 55-64 since the 1985-1989 period. More fluctuation is seen for patients aged 65-74 years old, but there is a general trend toward improvement, albeit at rather low levels of survival, between 1980-1984 and 2000-2004.

In order to consider the effects of late relapses in AML, we examined probability of surviving the next 5 years in patients who had already survived 1-5 years (*conditional survival*, see Figure 4). For patients aged 15-34 diagnosed in 2000-2004, relative survival within the subsequent 5 years rose from about 50% in the year of diagnosis to over 90% in the 5 years after diagnosis. The conditional 5-year relative survival increased from about 20% in the year of diagnosis to less than 80% 5 years after diagnosis for patients in the same age group in 1980-1984. Five-year conditional relative survival was close to 90% 5 years after diagnosis for patients aged 35-54 and 55-64 in the 2000-2004 calendar period, increasing from approximately 70% and 80%, respectively, in 1980-1984. Overall, 5-year conditional survival for patients who survived 5 years increased from about 65% in 1980-1984 to between 85 and 90% in 2000-2004. Thus, long-term survival for patients with AML who have survived for 5 years has improved.

In order to better examine long-term outcomes in patients with AML who achieve lasting remissions, we estimated 25-year relative survival for the 2000-2004 period (Figure 5). Relative survival decreases sharply in the first 5 years after diagnosis for all age groups, but then the curves begin to differ in shape.

Relative survival for patients aged 15-34 stabilized between 10 and 15 years after diagnosis at a level between 45 and 50%. Relative survival for patients aged 35-54 and 55-64 continued to decrease slowly over time even up to 25 years after diagnosis.

Patients aged 35-54 and 55-64 seem to have a sharp decrease in survival at 20-25 years after diagnosis.

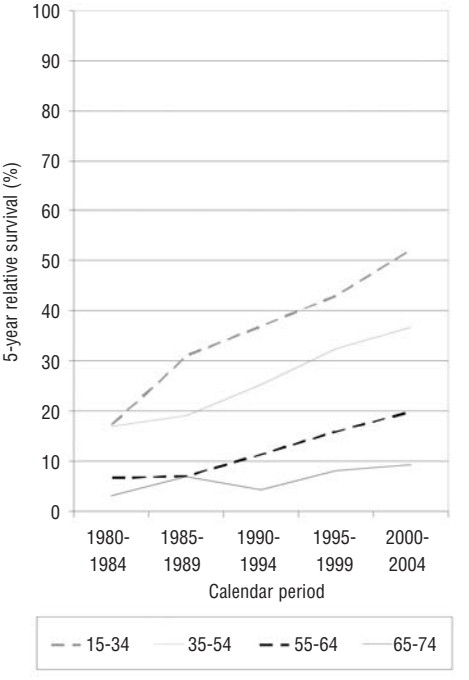

Figure 3. **Period estimates of 5-year relative survival of patients with acute myeloblastic leukemia by major age groups in defined calendar periods from 1980-1984 to 2000-2004.**

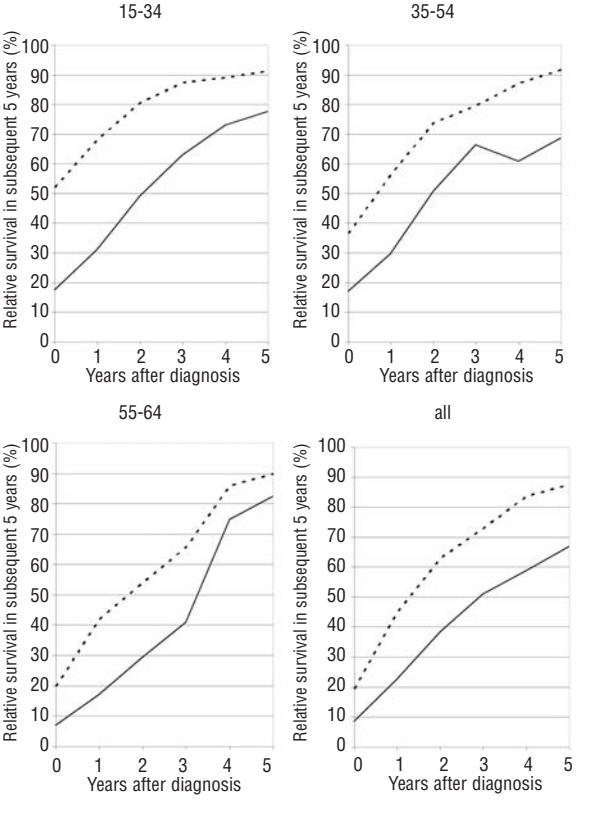

Figure 4. **Conditional relative survival in the subsequent 5 years among patients with acute myeloblastic leukemia by age group and year after diagnosis. Period estimates are for 1980-1984 (solid lines) and 2000-2004 (dashed lines).**

However, these patterns must be interpreted with caution as they are based on small numbers of long-term survivors.

Discussion

Improvements were made in the treatment of adult AML in the period between 1980-1984 and 2002-2004 in every age category except for the oldest patients. The greatest improvements were seen in patients aged 15-34, with 5-year relative survival increasing from less than 20% to approximately 50% and 10-year relative survival increasing from less than 15% to more than 45% between 1980-1984 and 2000-2004.

An increase in the case numbers of AML was observed in all age categories between 1980-1984 and 2000-2004. This primarily results from an increase in the population size, particularly in people aged 75 or older, rather than from an increase in the incidence of the disease or a change in diagnostics. The age-adjusted incidence of AML between 1975 and 2004 has varied from a minimum of 3.0 to a maximum of 4.0, with an average incidence for the period as a whole of 3.4 and an incidence of 3.3 in 2004.[18]

Despite the therapeutic improvement, even patients in the age groups with the best prognosis have less than a one in two chance of surviving 10 years after diagnosis. Furthermore, although, in 2000-2004, conditional relative survival within the subsequent 5 years was around 90% for 5-year survivors aged less than 65 years old at the time of diagnosis, decreases in relative survival continued to be seen for at least 25 years after diagnosis. Additionally, improvements in prognosis have not extended to patients older than 75 years of age and survival in patients aged 65-74 remains low. This is of particular concern given that more cases of AML occur in this age group than in any other, and that more than half of the patients diagnosed in 2000-2004 were over 65 years old.

Traditionally, the treatment for AML has been induction chemotherapy with a "7+3" regimen, which consists of 7 days of cytarabine and 3 days of an anthracycline such as daunorubicin, which followed by several cycles of consolidation therapy with high dose cytarabine[4] with or without autologous stem cell transplantation (SCT) or allogeneic SCT in first remission, depending on cytogenetic analysis, the patient's characteristics, and the availability of a donor. The "7+3" induction regimen, while highly effective at inducing remission, is also highly toxic, and quickly becomes less effective if dose reduction or delays are required. Improvements in supportive care, including the introduction of hematopoietic cell stimulating agents, better and more effective use of antimicrobials, and improved transfusion care have ameliorated some of the hardships of the induction regimen and contributed to improved survival, but the regimen remains suboptimal in some patients. Additionally, neither option for consolidation therapy is ideal. Relapse is relatively common after treatment with conventional chemotherapy, while allogeneic SCT is highly toxic and so cannot be applied to patients aged over 65 years old and results in a high incidence of treatment-related deaths.

In general, treatment of AML does not vary by subtype. However, APL is an exception. APL is usually treated with ATRA as well as chemotherapy. ATRA was introduced in the late 1980s and has been shown to improve survival in APL significantly,[3] but APL accounts for a minority of AML patients (approximately 5% of AML patients in the SEER database are identified as having APL) and, therefore, most of the improvement observed in our study is not due to the availability of ATRA.

Much of the improvement seen in AML survival over the 25 years between 1980 and 2004 is probably due to improved understanding of the prognostic significance of different cytogenetic alterations seen in AML, better and more judicious use of supportive care, and improvements in SCT. It has become clear that cytogenetic abnormalities have specific prognostic significance in AML. Patients with low risk disease can be treated with consolidation chemotherapy alone or with autologous SCT, sparing them the risk of allogeneic SCT, whereas patients with higher risk disease can immediately undergo allogeneic SCT in first com-

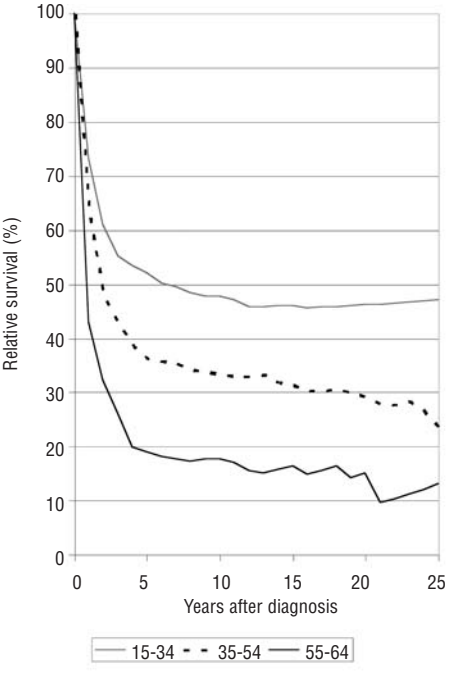

Figure 5. Relative survival over 25 years following the diagnosis of acute myeloblastic leukemia in patients in the three younger age groups. Period estimates for 2000-2004.

plete response, when the chances of cure are best.[1] High dose cytarabine as consolidation chemotherapy, first used in the 1980s and demonstrated to be superior to standard dose cytarabine in 1994,[4] improved survival in patients with AML during the 1990s as well. Reduced intensity allogeneic SCT has been shown to be useful in older patients with poor prognostic features, with good 1-year outcomes,[19] but longer term outcomes are not yet clear.

Allogeneic SCT was first introduced into clinical practice for the treatment of leukemia in the late 1970s. Initially, it was a highly dangerous therapy and its use was limited to patients under 40 years old who had otherwise untreatable disease.[20] As SCT became more routine, this age limit increased, although the risk of treatment-related mortality increases with age.[1,21] Improvements in survival in patients who underwent allogeneic SCT in the1980s through the late 1990s have been documented by several authors using data from the International Bone Marrow Transplant Registry.[22,23]

In addition, other factors may have improved the outlook for AML patients in need of transplant. The advent of international registries of potential stem cell donors and cord blood banks as well as improvements in immunosuppressive medications that allow non-HLA identical donors to be used, although at a higher risk, have enlarged the pool of donors. Improved supportive care techniques, including less toxic conditioning regimens, better treatment of and prophylaxis against graft-versus-host disease, and better treatment of infections in neutropenic patients have all led to improved survival for transplant recipients.[1]

Treatment of older patients with AML is a special problem for several reasons. First, many patients over 60 years old with AML are simply not offered chemotherapy of any sort. One study of patients aged over 65 showed that only 38% of older patients with AML received chemotherapy in 1999 and as few as 29% of patients aged 65 or older received chemotherapy in 1991.[24] Additionally, patients aged 75-84 were about half as likely to receive chemotherapy as those aged 65-74 and very few patients aged over 85 years old received chemotherapy.[24] This lack of treatment may be unjustified in many cases, as studies have shown that chemotherapy can extend the life expectancy of otherwise healthy older patients with AML.[25] Indeed, the increase in the number of patients aged 65-74 who received chemotherapy between 1991 and 1999 and possible continuation of the trend toward more aggressive treatment of older patients into the 21st century, may partially explain the increase in survival seen in this age group. However, older patients are more likely to have AML with poor prognostic features (poor prognostic cytogenetics, post-myelodysplastic syndrome AML, or treatment-related AML)[26] and are more likely to suffer toxic effects after treatment with standard chemotherapy, with treatment-related death rates of 15-19% occurring in patients older than 55 years of age.[27]

The results of our analysis pertain to patients with no prior malignancies, i.e. those who may have had treatment-related AML or AML arising from a myelodysplastic syndrome clone were excluded. Therefore, the survival observed may be slightly higher than that which would be observed if all cases were to considered. Despite the use of the large SEER database, some of the survival estimates have standard errors of close to 3%. Nevertheless, with the exception of the over 75-year old age group, all of the observed trends were highly statistically significant. A particular strength of our study is the application of period analysis which enabled assessment of the most recent improvements in survival which may not be observable using traditional cohort or complete analysis.

In summary, 5- and 10-year relative survival has improved substantially for younger AML patients over the past 25 years. The improvement was greatest in the 15-34 year age group, with highly significant improvements being seen in the 35-54, 55-64 and 65-74 year age groups as well. Survival is very poor and has not improved for the oldest age group. Given the large number of patients in the oldest age group and their poor prognosis, further research into the treatment of older patients with AML and greater awareness of treatment options are critical.

Authorship and Discosures

DP contributed to the interpretation of the data and was the primary author of the manuscript; AG provided input into interpretation of the data and revision of the manuscript; HB designed and carried out the data collection, contributed to the interpretation of the data, and to the revision of the manuscript. All authors read and approved the final version of the manuscript.

The authors reported no potential conflicts of interest.

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