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Improvements in the early death rate in 9,380 acute myeloid leukemia patients following initial therapy: a SEER database analysis

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Abstract

Background—Acute myeloid leukemia (AML) is treated with conventional induction chemotherapy shortly after diagnosis for most patients ≤ 65 years old. A recent report suggested a substantial decline in the early, or one-month, mortality rate in patients treated on clinical trials over the past 2 decades. It is unknown if a similar improvement has been observed in the general population.

Methods—We examined the one-month mortality in a large population-based series of 9,380 AML patients ≤ age 65 diagnosed and treated with chemotherapy between 1973 and 2010.

Results—We observed a significant decline in the one-month mortality rate from 18.7% among patients diagnosed from 1973–1977 (95% CI 16.4–21.2%) to 5.8% for those diagnosed in 2008–2010 (95% CI 4.5–7.6%) (p-value < 0.001). Median overall survival (OS) improved significantly from 6 months (95% CI 5–7) in 1973–1977 to 23 months (95% CI 16–20) in 2008–2010 (p-value < 0.001). Though age and geographic variation significantly influenced one-month mortality in 1973–1977, these differences in one-month mortality were no longer significant in AML patients treated more recently (2008–2010).

Conclusions—Over the past four decades, early mortality has become uncommon in younger patients (≤ 65 years) with newly diagnosed AML undergoing induction chemotherapy. It is encouraging that the improvements seen in one-month mortality in a selective cohort of clinical trial patients are also observed in a population-based analysis.

Keywords

Leukemia; epidemiology; outcomes; early death; treatment-related mortality

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Authorship

Contribution: All authors designed the study, analyzed and interpreted data, and participated in writing the manuscript; L.T. performed data collection and statistical analysis.

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Background

Without treatment, acute myeloid leukemia (AML) is uniformly fatal in weeks to months.[1] For the past 40 years, most younger (≤ 65 years) patients with AML receive treatment combining infusional cytarabine with an anthracycline (most commonly daunorubicin, using the 7+3 regimen) shortly after diagnosis.[2, 3] With this combination, the complete remission (CR) rate in patients younger than age 60 ranges between 60 and 80%.[4, 5] The CR rates in patients over age 60 are significantly lower.[6, 7] Primary refractory disease is reported in approximately 15 to 30% of younger patients, depending on the series and type of induction therapy. The remaining AML patients experience a fatal complication within one month of diagnosis (known as early death or treatment-related mortality).[8–10] Death most commonly occurs from infectious or bleeding complications related to cytopenias. The risk of mortality decreases significantly four weeks from the time of treatment initiation.[10]

Retrospective data combined from two large cohorts of patients treated on clinical trials indicate that one-month mortality has declined significantly over the past two decades.[11] Reasons for this decrease may relate to improved supportive measures during the period of marrow aplasia, including empiric initiation of potent, broad-spectrum antibiotics and antifungals, strict adherence to guidelines regarding management of neutropenic fever, and improved transfusion support prior to count recovery.

It remains unknown, however, whether the decline in early mortality rates reported among highly selected patients treated on clinical trials and in tertiary care centers has also been observed in the general population. It has been estimated that only 5 to 10% of AML patients participate in clinical trials.[12] In this study, we set out to examine the one-month mortality in a large population-based series of patients with AML undergoing chemotherapy using a representative national sample.

Methods

Study Population

We obtained from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI) information regarding all 10,940 patients diagnosed with a first primary AML [International Classification of Disease for Oncology, 3rd Edition, (ICD-O-3) histology codes 9840, 9861, 9865, 9867, 9870–9874, 9891, 9895–9897, 9910, 9920, 9930, 9931] between the age of 18 and 65 during the period January 1, 1973 through December 31, 2011 in 9 SEER regions [San Francisco-Oakland, Connecticut, Detroit (Metropolitan), Hawaii, Iowa, New Mexico, Seattle (Puget Sound), Utah, Atlanta (Metropolitan)] for which data was available since 1973. We excluded patients with acute promyelocytic leukemia (ICD-O-3 code 9866). The cancer registrar recorded AML cases based on the interpreting pathologist's documentation. We excluded, in a hierarchical manner, 54 cases who were diagnosed by death certificate only, 81 who had zero days of survival, and 1,425 who did not have a record of ever having received chemotherapy. The final study population included 9,380 patients. For each AML case, we obtained information routinely abstracted from the medical record regarding patient age at diagnosis, race/ethnicity, stage of diagnosis, as well as treatment within the first 12 months after diagnosis.

We also obtained vital status as of December 31st, 2011 and the underlying cause of death from the death certificate.

For analysis of effect of time period on one-month mortality, we divided the cohort into 5-year increments based on date of diagnosis. For analysis of effect of geographical location, we divided the 9 SEER regions into three categories based on one-month mortality from 1973–1977: lowest early death rate (Detroit Metropolitan); intermediate early death [Atlanta (Metropolitan), Connecticut, Hawaii, Iowa, San Francisco-Oakland SMSA, Seattle (Puget Sound), and Utah]; and highest early death rate (New Mexico). We assessed the one-month mortality in these three cohorts over time, using the same five-year increments.

Statistical analysis

We used the software program SEER*Stat (version 6.7, NCI, Bethesda, MD) to calculate overall survival (OS) rates, median OS, one-month mortality rate (and associated 95% confidence intervals) from the vital status recorded in SEER with follow-up through December 31, 2010 by year of diagnosis. We calculated the one-month mortality rate event as death occurring within one month of the recorded date of AML diagnosis.

Linear regression weighted on standard error was used to measure and test for statistical significance of the annual trend in one-month mortality rates across time periods. Regressions and calculations of R^2 and β statistics were carried out using SAS software version 9.3 (SAS Institute, Cary, North Carolina). All P values reported were two-sided, and those that were <0.05 were considered to be statistically significant. Statistical analysis was performed by L.T. This project was overseen by the institutional review board of the Cancer Prevention Institute of California.

Results

Baseline Characteristics

The baseline characteristics of the 9,380 patients who met the inclusion criteria between 1973 and 2010 are presented in Table 1. As expected, there was an elevated male to female ratio (1.23:1), and non-Hispanic whites represented the majority of patients (75.4%). The incidence of AML increased with advancing age, while the median age at diagnosis over the study period remained unchanged (50 years for entire cohort). The incidence rate of AML remained stable when measured in five-year increments from 1973 to 2010. The one-month mortality for the entire cohort was 10.4% (95% CI 9.8–11.0).

We observed changes in the composition of AML diagnoses with respect to histologic classification over time. The introduction of the cytogenetic-based World Health Organization classification in 2001 and the associated change in diagnostic codes to ICD-O-3 provided more granularity in AML subtyping (Supporting Table 1). The new classification of AML entities led to a decrease in the percentage of patients coded as 9861/3 (acute myeloid leukemia) from 78.6% in 1973–2000 to 46.4% in 2001–2010. For those entities where cytogenetic-based classification is not relevant, such as 9840/3 (acute erythroid leukemia), the percentage of patients reported remained stable (2.1% from 1973–2000 and 2.1% from 2001–2010).

Effect of time period of diagnosis on median OS and one-month mortality

We assessed whether time period of diagnosis affected the median OS. Throughout the study period, the median age at diagnosis ranged between 50 and 52 years (Table 2). During this time, however, we observed a significant improvement in the median OS from 6 months (95% CI 5–7) in patients diagnosed between 1973 and 1977 to 18 months (95% CI 16–20) in patients diagnosed between 2003 and 2007. At the time of analysis, patients diagnosed in 2009 and 2010 did not have adequate follow up to calculate their median OS, but the median OS for patients diagnosed in 2008 had improved further to 23 months (95% CI 20–31; Table 2 and Figure 1) (p-value < 0.001). Linear regression analysis confirmed a strong linear trend for improvement in median OS over time (Figure 1; $R^2 = 0.86$).

Next we determined the one-month mortality rate for AML patients who received chemotherapy (Table 2 and Figure 2). Our analysis revealed a significant temporal decline in the one-month mortality from 18.7% (95% CI 16.4–21.2) between 1973 and 1977 to 7.2% (95% CI 6.0–8.6) between 2003 and 2007. The lowest one-month mortality was noted in patients diagnosed between 2008 and 2010 (5.8%, 95% CI 4.5–7.6). Weighted linear regression analysis revealed a strong linear trend in the one-month mortality rate (Figure 2; $R^2 = 0.78$), with a steady annual decrease in the rate of approximately 0.4% per year ($\beta = 0.3755$). Notably, we observed a similar decline in two-month mortality over the study period (data not shown). Together, in our cohort over time, we observed a parallel increase in median OS and decrease in one-month mortality.

Impact of age on one-month mortality rates

To examine the effect of age on the one-month mortality rates of AML patients, we divided the cohort into three age groups spanning approximately 15 years each (Supporting Table 2). For all three age groups, the one-month mortality was highest in 1973–1977, with older patients experiencing the highest early death rates (Supporting Table 2 and Figure 3). Over the study period, a significant improvement in the one-month mortality rates was observed in all age cohorts. The largest absolute improvements were noted in older patients (approximately 15% absolute decrease in one-month mortality for patients aged 51–65 over entire time period). Linear regression analysis showed a strong trend for decrease in one-month mortality in all age cohorts (Figure 3). For all age cohorts, one-month mortality rate was lowest in the most recent time period (2008–2010), without significant differences in one-month mortality among age cohorts (p-value = 0.3347 between the 51–65 year cohort and 18–35 year cohort; p-value = 0.2531 between 36–50 year cohort and 18–35 year cohort). In summary, one-month mortality rates have improved among AML patients ≤ 65 years, with particular benefit noted in patients between the ages of 51 and 65 years at diagnosis.

Geographic variation in one-month mortality rates

We next examined whether location at diagnosis had an effect on one-month mortality. We examined the one-month mortality in the nine SEER regions, and found improvement over time in each region (Supporting Figure 1). We further divided the nine SEER regions into 3 groups based on one-month mortality in the earliest time period included in our analysis (1973–1977); then the one-month mortality in these 3 groups was evaluated over time. Little

absolute improvement in the one-month mortality rate was observed in the group with initial low early death, decreasing minimally from 9.1% (95% CI 3.5–22.4%) between 1973 and 1977 to 7.1% (95% CI 2.7–17.9%) between 2008 and 2010 (Supporting Table 3 and Figure 4). Conversely, our analyses revealed significant declines in one-month mortality in the cohorts of patients with high and intermediate early death rates. This mismatched improvement of the one-month mortality resulted in a convergence of the early death rates observed among AML patients from all geographic areas in the 2008–2010 period (Figure 4). As such, our results demonstrated a lack of significant differences in one-month mortality in the 2008–2010 period ($p = 0.4616$ for intermediate compared to high early death locations; $p = 0.9119$ for low compared to high early death locations).

Discussion

Though induction chemotherapy for patients with AML has not changed substantially since its introduction in 1973, our population-based study demonstrates that one-month mortality in 9,380 patients ≤ 65 years undergoing initial chemotherapy has decreased by nearly 70% over the same time frame. This improvement in one-month mortality was noted in all patient cohorts, independent of age or geographic region at diagnosis. Our results also reveal that one-month mortality has particularly improved in patients between 51 and 65 years, and from certain geographic areas with high and intermediate initial one-month mortality rates.

The reasons for the decreases in one-month mortality remain largely unexplained, as there is no clear inflection point in the observed improvement over time. Recently, significant improvements in survival attributable to supportive care were reported in patients with hematologic malignancies after allogeneic transplant, and similar mechanisms likely account for the improvements observed here in AML patients.[13] Bleeding and infections are the most common issues leading to treatment-related early death; relevant advances in the management of AML patients undergoing aggressive chemotherapy over this time period include the use of rigorous prophylactic platelet transfusions and breakthroughs in the management of infectious complications, particularly fungal disease.[14–16]

Our observations are particularly powerful since the study dataset was derived from a large, representative, national cohort identified from the high-quality SEER program. The program covers 28% of new cancer diagnoses in the United States, though the coverage was lower in 1973 when SEER was established and when the data for this study began collection. Additionally, the patient characteristics in our cohort have generally remained similar over time (Table 1). Although improvements in early death rates have been reported in patients participating in AML clinical trials,[11] such beneficial effects in outcomes are frequently not observed in subjects receiving therapy in the “real world.”[17] Additionally, only 5–10% of patients with AML in the United States are estimated to participate in clinical trials, potentially limiting the generalizability of those findings.[12] In fact, in a highly curable subtype of AML, acute promyelocytic leukemia (APL), a clear disparity exists between the low early death rates observed on clinical trials (approximately 10%) compared to the much higher rates seen in population-based analyses (ranging from approximately 15–30%).[18–21] These differences in outcomes exist even though recent data indicate that over 70% of newly diagnosed APL patients participate in research protocols.[22] However, in contrast to the

findings in patients with APL, our results in a cohort of AML patients drawn from the general population find improvements over time in one-month mortality comparable to those observed in a large clinical trial-based population.[11] An unusual finding in our study was the large variability in one-month mortality based on geographic location in the earliest time periods; further study should be devoted to answering this question.

Our study had the benefit of being large and representative, but has several important limitations. SEER data do not contain details regarding what type of chemotherapy regimen patients received (including potential need for re-induction chemotherapy), compliance to therapy, nor when chemotherapy was started. Therefore, if delays existed in diagnosis or initiation of treatment, the one-month survival rate we reported might instead be a less meaningful 2 or 3-week survival rate for some patients; however, we did also observe a decrease in 2-month mortality over the same time period, which suggests that the trend in improvement is valid regardless of variations in timing of initiation of chemotherapy. The SEER dataset also does not include standard baseline characteristics often used to risk-stratify AML patients such as performance status, white blood cell count, percentage of bone marrow blasts, and cytogenetics, though it seems unlikely that these characteristics would vary significantly over time in the population.[5] During the study period, the percentage of blasts needed to make the diagnosis of AML changed from 30 to 20%; however, this change in classification would affect any longitudinal study of AML patients.

Although the median age at the time of AML diagnosis is 67, we chose to limit our study population to patients between the ages of 18 to 65 years.[23] First, we performed our analyses only in patients confirmed to have received at least one dose of chemotherapy, which is not universally considered in patients over the age of 65 at diagnosis. In fact, a recent analysis of a SEER-Medicare linked database of patients over the age of 65 with newly diagnosed AML demonstrates only 40% of these patients receive chemotherapy (Medeiros, BC, personal communication). Also, the cohort of 9,380 patients we selected likely received relatively homogenous therapies, as population-based registries have previously shown that only 5% of patients younger than age 65 are not treated with induction chemotherapy.[3, 24] Finally, it has been previously demonstrated that advanced age in AML is associated with disproportionately high early mortality, decreased treatment rates, and decreased use of conventional induction chemotherapy with preference for lower-intensity regimens, such as low-dose cytarabine or hypomethylating agents.[25–28] The goal of our analysis was to examine patients likely to have undergone standard induction chemotherapy, and patients over 65 likely did not meet that criterion.[29] We would expect that only a small minority of patients in our cohort would have been treated upfront with hypomethylating agents since azacitidine was only FDA-approved in 2004 and is typically used in patients over the age of 60.

Overall, the improvements in early mortality and OS observed in our population-based cohort of AML patients are reassuring and consistent with clinical trial results.[11] Previous analyses have determined that age and performance status are the two most important variables influencing treatment-related mortality in AML.[10] Our results fail to demonstrate a significant inflection point in the early death rates or OS for younger AML patients, suggesting that advances in routine clinical care during the study period are responsible for

the progressive and continuous improvements we observed. Finally, our results suggest that concerns regarding increased early mortality should not be a deterrent to induction chemotherapy in patients under the age of 65 with AML.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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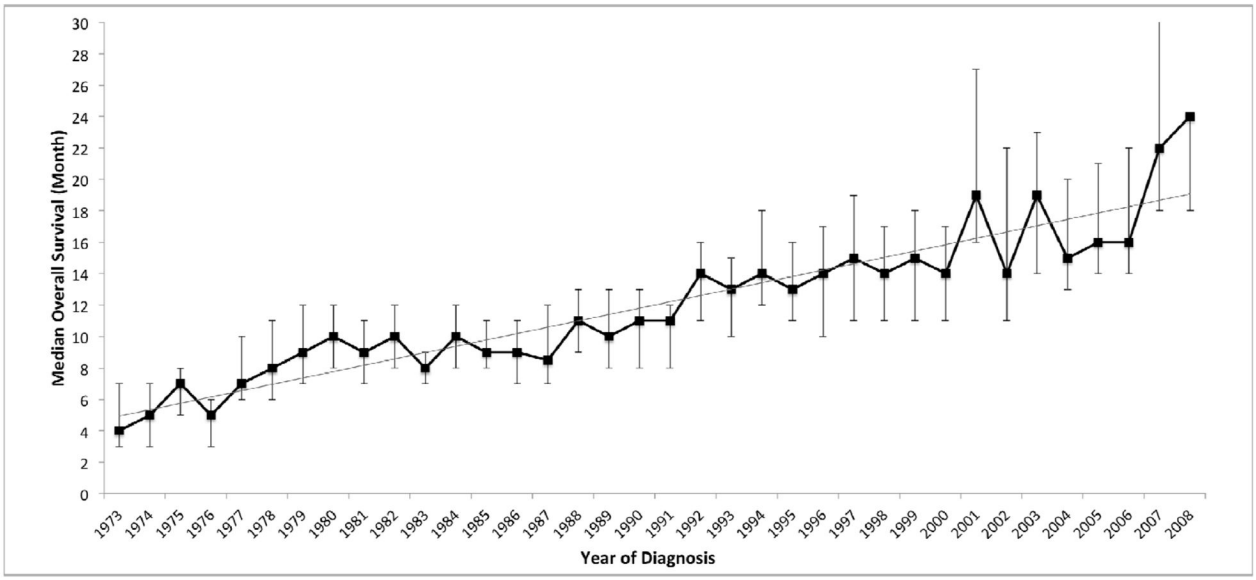

Figure 1.

Median overall survival (months, %95 CI) for AML patients, by year of diagnosis, SEER 9 Registries, 1973–2010. Median survival was not available for patients diagnosed in 2009 and 2010. Test for linear trend: $R^2 = 0.86$. $\beta = 0.4042$.

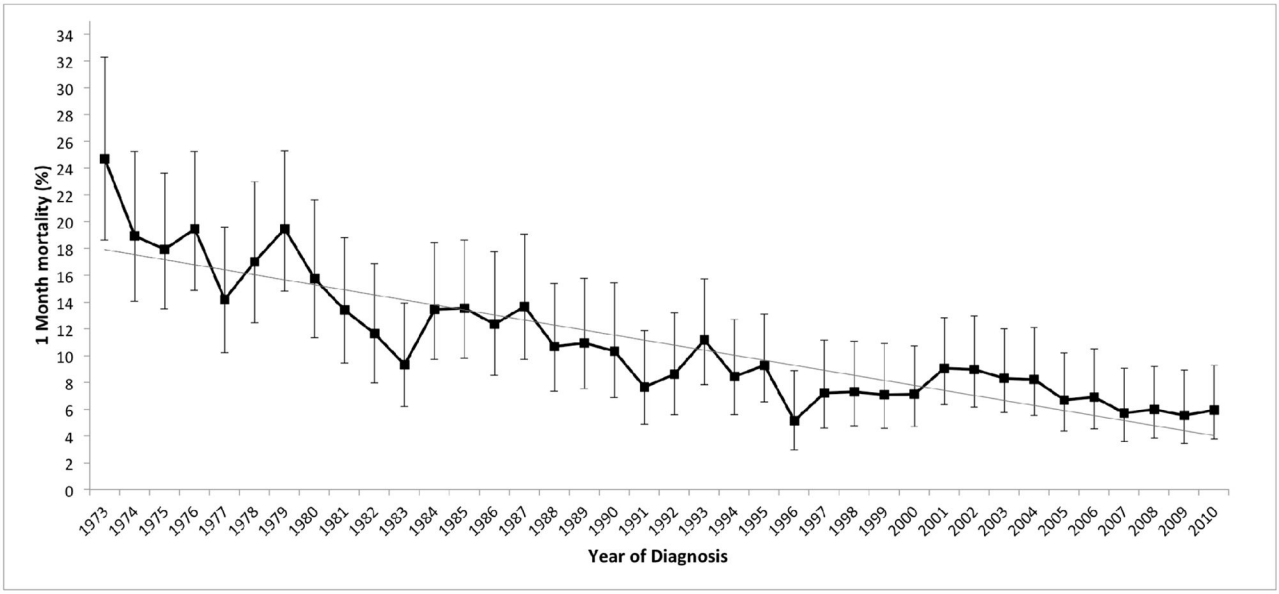

Figure 2.

One-month mortality (%, 95% CI) for AML patients, by year of diagnosis, SEER 9 Registries, 1973–2010. Test for linear trend by weighted linear regression analysis: $R^2 = 0.78$, $p < 0.001$. $\beta = -0.3755$.

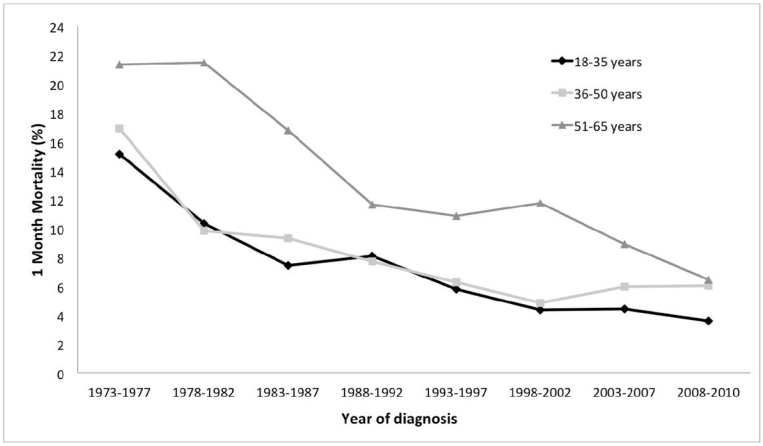

Figure 3.

One-month mortality (%) for AML patients, by year of diagnosis and age at diagnosis, SEER 9 Registries, 1973–2010. Statistics for 18–35 years: $R^2 = 0.8500$ and $\beta = -1.4507$; for 36–50 years, $R^2 = 0.6934$ and $\beta = -1.3138$; for 51–65 years, $R^2 = 0.9063$ and $\beta = -2.1761$.

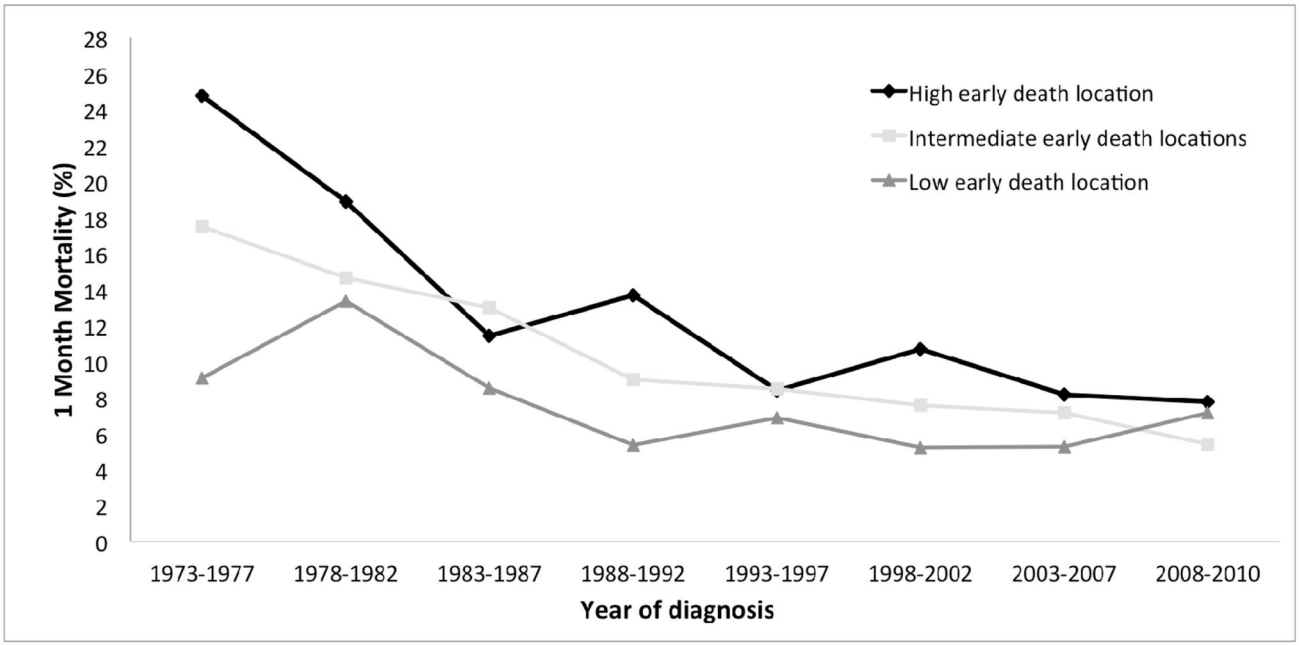

Figure 4.

One-month mortality (%) for AML patients, by year of diagnosis and location, SEER 9 Registries, 1973–2010. Rate of early death was determined in each location during earliest time period (1973–1978). Statistics for high early death location, $R^2 = 0.7626$ and $\beta = -2.1482$; for intermediate early death locations, $R^2 = 0.923$ and $\beta = -1.6536$; for low early death location, $R^2 = 0.4381$ and $\beta = -0.7434$.

Table 1

Demographic and clinical characteristics for patients diagnosed with AML, SEER 9 registry, 1973–2010.

Baseline characteristic	Population (n = 9,380)
Age at diagnosis (≥18 to ≤65): Median	50
18–25	815 (8.7%)
26–35	1233 (13.1%)
36–45	1673 (17.8%)
46–55	2406 (25.7%)
56–65	3253 (34.7%)
SEER registry	
Atlanta (Metropolitan) - 1975+	830 (8.8%)
Connecticut - 1973+	1304 (13.9%)
Detroit (Metropolitan) - 1973+	1652 (17.6%)
Hawaii - 1973+	480 (5.1%)
Iowa - 1973+	1117 (11.9%)
New Mexico - 1973+	493 (5.3%)
San Francisco-Oakland SMSA - 1973+	1506 (16.1%)
Seattle (Puget Sound) - 1974+	1390 (14.8%)
Utah - 1973+	608 (6.5%)
Sex	
Female	4206 (44.8%)
Male	5174 (55.2%)
Race/ethnicity	
Non-Hispanic White	7077 (75.4%)
Non-Hispanic Black	815 (8.7%)
Hispanic	599 (6.4%)
Non-Hispanic Asian or Pacific Islander	820 (8.7%)
Non-Hispanic American Indian/Alaska Native	57 (0.6%)
Unknown	12 (0.1%)
Rural-Urban Continuum	
Nonmetropolitan	1291 (13.8%)
Metropolitan	8089 (86.2%)
Year of diagnosis	
1973–1977	1011 (10.8%)
1978–1982	1033 (11.0%)
1983–1987	1113 (11.9%)
1988–1992	1120 (11.9%)
1993–1997	1294 (13.8%)
1998–2002	1425 (15.2%)
2003–2007	1475 (15.7%)
2008–2010	909 (9.7%)

Table 2

One-month mortality after diagnosis of AML, by period of diagnosis, SEER 9 registry, 1973–2010. CI = confidence interval.

Period	Median Age at Diagnosis	Median Overall Survival (months, 95% CI)	1 Month Mortality (%, 95% CI)
1973–1977	52	6 (5–7)	18.7 (16.4–21.2)
1978–1982	51	10 (8–10)	15.5 (13.4–17.8)
1983–1987	51	9 (8–10)	12.5 (10.7–14.6)
1988–1992	50	11 (10–12)	9.6 (8.1–11.5)
1993–1997	50	13 (13–15)	8.3 (7.0–10.0)
1998–2002	50	16 (14–17)	7.9 (6.6–9.5)
2003–2007	52	18 (16–20)	7.2 (6.0–8.6)
2008–2010	52	23 (20–31)	5.8 (4.5–7.6)