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Early mortality in acute myeloid leukemia

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ABSTRACT

The Southwest Oncology Group (SWOG) described the expected early mortality rate (EMR) for patients with non-M3 AML by age enrolled in clinical trials, but it is unclear how generalizable this data is. We sought to compare SWOG's reported EMR to that of the general population by utilizing the case listing session of SEER 18 matched to the accrual periods of the SWOG studies. 26,272 patients were identified within SEER compared to 968 in the SWOG cohort with mortality data. The EMR was 26.7% (7022 events) in the SEER cohort versus 12.2% (116) in the SWOG cohort. The EMR was higher in the SEER cohort in every studied age group and definition of EMR. Stepwise logistic regression analysis identified increasing age, black race (OR 1.15, CI 1.03-1.29, $p < 0.01$), and monocytic differentiation (OR 1.55, CI 1.27-1.89, $p < 0.01$) as predictors of higher EMR. This study demonstrates that EMR in patients with non-M3 AML is higher in the general patient population than reported in SWOG clinical trials.

1. Introduction

Acute myeloid leukemia (AML) is the most common type of leukemia in adults with an estimated incidence of 3.7 per 100,000 persons [1]. In the United States, an estimated 14,000 new cases of AML were diagnosed and 10,000 deaths were reported in the year 2013 [2]. The overall prognosis of AML is poor with 5-year relative survival rate of 17–19% [3,4].

Over the past 30 years, the prognosis of AML has improved due to the fine-tuning of supportive care as well as alterations to pre-existing chemotherapeutic regimens [5]. However, this improvement has been seen mostly in children and young adults and those with favorable cytogenetic and molecular abnormalities with little evidence of improvement in elderly individuals or those with adverse prognostic markers [5].

A significant proportion of deaths related to AML occur within the first month of diagnosis [6]. AML is considered an oncologic emergency due to the potential for early mortality from infection, hemorrhage, or sequelae of hyperleukocytosis [7]. However, there is limited data regarding the incidence of early death in these patients. A previously published study based on a Southwest Oncology Group (SWOG) cohort of 5 clinical trials showed an estimated early mortality rate (EMR) of 12% [8]. However, real world data from experience outside of clinical trials is lacking. To fill this knowledge gap, we aimed to use a large national cancer registry database to estimate the frequency of early mortality in patients with newly diagnosed AML in the United States and compare these findings with the SWOG cohort.

2. Materials and methods

Our epidemiologic study utilized case listings from 18 population-based regional cancer registries in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program from 1973 to 2010 [9]. SEER 18 covers approximately 28% of the US population. SEER registries maintain data including patient demographics, incidence, mortality, primary site, tumor structure, and follow-up information. The SEER database classifies cancer histology and topography information on the basis of the third edition of the *International Classifications of Diseases for Oncology* (ICD-O-3).

For our study, we identified patients 18 years of age and older diagnosed with non-M3 AML (defined as ICD-O-3 codes 9840/3, 9861/3, 9867/3, 9872/3, 9873/3, 9874/3, 9891/3, 9895/3, 9896/3, 9897/3, 9910/3, 9920/3) between 1990 and 2005 from SEER 18. We chose this time parameter and patient profile to match the accrual periods of the SWOG studies. We examined EMR of these patients overall and by age group and then compared them with those reported by SWOG. To best address induction therapy related mortality (EMR) in the SEER cohort and to account for the lag time between initial diagnosis and beginning of induction therapy, we used two definitions of EMR to include deaths within 1 month (EMR1) and deaths within 2 months of diagnosis (EMR2). We calculated survival rates at 1 month and 2 months overall and for levels of each covariate using the actuarial method. EMR was then calculated by subtracting the survival rate from 1. In contrast to the SEER cohort, EMR in SWOG studies was defined as death within 30 days of initiation of induction chemotherapy, not diagnosis. The difference between the EMR in the two groups was analyzed using Fisher's Exact test.

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We calculated the EMR1 and EMR2 in the SEER cohort and stratified by different covariates including age at diagnosis, gender, year of diagnosis, race and AML subtype based on ICD-O-3 codes. The differences in EMR1 and EMR2 among different levels of the covariates were analyzed using Fisher's exact test. We also performed stepwise logistic regression analysis to identify the predictors of early mortality in the SEER study cohort. Analyses were conducted with SEER*Stat 8.1.2, GraphPad Prism 6, and Statistical Package for Social Sciences (SPSS) 21.0 (IBM Corporation, Armonk, NY). All p-values were based on 2-sided hypothesis tests.

3. Results

A total of 26,272 patients with AML were identified in the SEER registry using the study criteria, of which 54% were males and 85% were whites (Table 1). The SEER EMR rate was 27% ($n = 7022$) within one month and was 38% ($n = 10{,}068$) within two months of diagnosis. In comparison, the SWOG cohort had a total 968 patients from 5 different clinical trials, of which 55% were male and 89% were whites. In contrast to our results, the SWOG cohort had an EMR of 12% ($n = 116$). The difference of EMR between the two cohorts was statistically significant ($p < 0.001$).

The age distribution and mortality by age for the SEER and SWOG cohorts are compared in Table 2. A marked difference was noted when comparing the distribution of AML patients in the extremes of age. Patients with AML <56 years account for 26% of the SEER cohort, while patients in the SWOG cohort <56 years represent 38% of the SWOG cohort. At the other end of the spectrum, 32% of patients in the SEER cohort were >75 years; in contrast, patients >75 years accounted for 8% of the SWOG cohort. In both cohorts, increasing age was associated with a progressive rise in EMR. For the SEER cohort, the EMR1 rose from 12% in patients <56 years to 42% in patients >75 years (OR 5.81, 95% CI (5.32–6.35), $p < 0.01$) (Table 3). Correspondingly, the SWOG cohort showed a rise from 3% to 32%.

Table 3 summarizes the EMR1 and EMR2 in the SEER cohort stratified by age, gender, race, year of diagnosis and AML subtype based on ICD-O-3 codes. Univariate analysis showed statistically significant differences in EMR across different age groups, races and AML subtypes. Among AML subtypes, acute myelomonocytic leukemia was associated with a substantially increased risk of early mortality. No significant differences were seen in terms of year of diagnosis (stratified in groups) or gender.

Table 4 shows the results of a stepwise logistic regression analysis designed to evaluate the prognostic ability of various factors on early mortality among patients in the SEER cohort. Multivariate analysis confirmed that age group ($p < 0.01$), race ($p < 0.01$) and AML subtype ($p < 0.01$) were the predictors of early mortality in the study population. Specifically, monocytic differentiation of AML, black race, and increasing age were predictors of early mortality.

4. Discussion

Our analysis of a large, unselected patient cohort from the SEER database revealed an EMR of 27% at 1 month and 38% at 2 months in newly diagnosed patients with AML. This was significantly higher than the EMR of 12% reported from the SWOG cohort. This difference in EMR was seen across all age groups and regardless of the definition of EMR used in the SEER cohort. Also, a greater proportion of elderly AML patients were seen in our study in comparison to the SWOG cohort [8].

The significant difference in EMR between the SWOG and SEER cohorts can be attributed to several factors. Patient selection factors may bias toward better outcomes in the clinical trial data. Clinical trials are conducted among cohorts of highly selected patients with few co-morbidities [10]. Clinical trials are conducted in highly specialized centers with greater availability of expertise and a variety of therapeutic options. Patients in highly specialized centers are closely followed and any therapy related complications are identified and treated early, which may not happen in community treatment centers. Although patient selection criteria likely contributes to SWOG's EMR, the large difference noted in EMR between SWOG and SEER provides evidence that the general population's EMR can be improved by increased referral to specialized leukemia centers and improved standard of care for induction therapy in community centers.

An important patient selection factor when considering clinical trial data is the lag time between the date of diagnosis of AML and the initiation of induction therapy, which creates the potential for guarantee time bias. As noted in our analysis, the definition of EMR used in the SEER cohort is different from the definition of EMR used in SWOG cohort, which could contribute to the difference in EMR noted. To attempt to overcome this in the SEER cohort, we examined EMR at two time points, EMR1 and EMR2, and showed consistent results regardless of the time point used. The use of two different endpoints to define EMR was done to best match SWOG's cohort by addressing the lag time between initial diagnosis and beginning of induction therapy.

Both the SEER and SWOG cohorts showed rising EMR with age. This supports age as a poor prognostic factor in AML, which could be due to worsening performance status and the increased incidence of unfavorable cytogenetic and molecular profiles with advancing age [8,11]. Similar findings have been reported by a smaller Swedish population-based study [12]. In addition, a population-based study of acute promyelocytic leukemia (APL) in the US revealed a similar correlation between advancing age and higher EMR [10].

There was no significant change in EMR1 and EMR2 over time when stratified by different years of diagnosis (between 1990 and 2005). In a similar SEER based study for APL, only a modest improvement in EMR rates was seen from 1992 to 2007 for APL [10]. The authors then contrasted their population-based results against the dramatic reduction in EMR reported by studies based on clinical trial data. Our findings are in sharp contrast to a recent study based on clinical trial data from SWOG and MD Anderson showing a significant decline in EMR for newly diagnosed AML from 1991 to 2009 [13]. As previously noted, the management of complications during induction therapy is likely better for patients enrolled in clinical trials at specialized centers.

The results of the stepwise logistic regression analysis (Table 4) present several finer points that could serve as prognostic factors for predicting EMR in individual AML patients. As an independent variable, black patients had a higher EMR, and a potential explanation is the racial disparity seen in the treatment of cancers in the general US population. The worsened survival for black patients in Table 4 appears to contradict the lower EMR seen for blacks than whites (25.9% versus 27.3%) in Table 3. However, the median age of presentation was significantly lower for blacks (63 years) versus whites (70 years) ($p < 0.01$), which has been controlled for in the multivariate analysis. Among the non-M3 AML subtypes, acute monoblastic and monocytic leukemia (AMML), ICD-O-39891/3, carried the highest risk of early mortality. The high EMR seen in AMML could be explained by the association of monocytic differentiation of AML with early disseminated intravascular coagulation (DIC), which could be directly responsible for a higher EMR [14]. While our study reveals that AMML has a higher risk of early mortality, the prognosis for overall survival of AMML is no worse than other non-M3 AML [15]. Another important observation from the analysis is that gender does not play a role in risk of EMR in AML patients.

Population based registries provide data that complements the findings of basic science studies and clinical trials, which are essential for establishing recommendations for managing patients [16]. Additionally, our study illustrates the need for population based registries to become more robust in order to answer complicated health questions. If SEER provided data on which AML patients received induction chemotherapy, it would allow us to make a