Review

How Center Volumes Affect Early Outcomes in Acute Myeloid Leukemia

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Abstract

Early mortality (EM) is all too frequent during induction chemotherapy for acute myeloid leukemia. Older patients shoulder an undue amount of this burden as a result of the inherent biology of their disease and increased comorbidities. EM rates in academic centers have seen a sharp decline over the past 20 years; however, data from population-based registries show that EM rates for the general population have significantly lagged behind. In this review, we analyze the data available on EM in academic centers and the general population, explore recent improvements in supportive care and the use of predictive models, and finally investigate the relationship between case volume and complications during chemotherapy.

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Introduction

Acute myeloid leukemia (AML) is the most acute common leukemia in adults, with an incidence of 3.7 per 100,000, and is primarily a disease of older adults, with a median age at diagnosis of 69 years.[1,2] Outcomes for AML worsen with age, as the 5-year overall survival (OS) rates for younger adults are approximately 50% and are only 3% to 8% for those older than 60 years.[3,4] Unfortunately, clinical outcomes for the majority of AML patients have not improved significantly over the past 40 years.[5] Outcomes for older adults with AML are poor because both the biology of the disease and the overall health of the patient change with age.[6] Older patients are more likely to have AML with increased expression of multidrug resistance proteins, be therapy related, and have unfavorable cytogenetics and/or molecular features including *TP53* mutations, and their disease is more likely to arise from myelodysplastic syndrome or other hematological disorders, making it more resistant to chemotherapy.[6-14]

Many older patients with AML have numerous comorbidities and poor performance status (PS), which makes them more vulnerable to excess toxicity from intensive induction chemotherapy. The combination of excess toxicity and biologically resistant disease makes early mortality (EM), or death during within the first 4 weeks, a common complication of AML in older patients.[6,15,16] The challenges presented by EM and resistant disease have influenced who is offered induction chemotherapy and have led to age cutoffs around 70 years.[17,18] Alternative induction strategies, such as clofarabine, laromustine, decitabine, and tipifarnib, in this patient population have been met with modest success at best. Other variations have also been explored, but again without any clear advantage.[19-27] Improvements in supportive care during intensive induction therapy and appropriate selection of older patients offered intensive induction therapy, with treatment decisions not only made on the basis of chronologic age, have improved outcomes in EM and can translate to improved survival.[28]

Here we explore the incidence of EM for AML and acute promyelocytic leukemia (APL) in academic centers and the general population. We review the improvements made in supportive care that have facilitated improvements in EM in academic centers. Finally, we consider the predictive tools utilized for EM during induction therapy and how these tools, along with clinical experience, can improve outcomes in older patients with AML.

Incidence and Trends in EM

In spite of the focus on supportive care in treatment of AML, EM remains a significant problem for older patients with AML.[2,6,29] EM is most commonly due to infection, hemorrhage, or the sequelae of hyperleukocytosis. A landmark study of 5 Southwest Oncology Group (SWOG) clinical trials by Appelbaum et al[6] was among the first to demonstrate that older patients with non-M3

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AML are more susceptible to EM and reported an EM rate of 12.1% (Table 1).[2,6,15,16,30] They also clearly demonstrated a relationship not only between age and EM but also between PS and EM. For example, the mortality of someone in age group 66 to 75 years varied on the basis of PS from 12% with a PS 0% to 47% with a PS of 3. A subsequent study of clinical trial cohorts by Othus and colleagues demonstrated significant improvements in EM among all age groups, with an EM rate of 3% in the SWOG cohort for 2009 compared to 18% for the cohort in 1991. The median age of the patients in the study by Appelbaum et al[6] was 61 years, with 37% of the patients aged > 65 years. The median age of the patients in the SWOG cohort by Othus and colleagues was 67 years (range, 23-89 years) for patients who had treatment-related mortality (TRM) and 56 years (range, 17-87 years) for patients who did not have TRM. The median age of patients in this study for the years 1991-1995 was 64 years compared to 49 years for the years 2006-2009. This difference in age could contribute to the decline noted in EM from 1991 to 2009. The authors also hypothesized that improvements in supportive care at experienced academic cancer centers facilitated the improvements observed in EM over time and that more older patients with AML may be candidates for intensive induction therapy at experienced centers.[15,31]

Because many clinical trials using variations of standard induction chemotherapy for AML exclude older patients, and the few that include older patients select for PS, AML type, and comorbidities, data on EM in the general population are needed to complement that presented by clinical trial groups.[32,33] Juliusson et al[2] used a Swedish population-based AML registry to show that overall EM was 19.3% among Swedish AML patients. Hahn et al[16] used a US population-based cancer registry to demonstrate that the EM rate among non-M3 AML patients was 26.7% in the general US population (Table 1). When reviewing literature on EM in AML, it should be noted that 3 different terms are used to describe death within the first month (TRM, EM, and early death). These different terms are used depending on author preference and whether the mortality is related to therapy (TRM) or just mortality within a defined time period of 1 or 2 months (EM or early death). EM reported from clinical trial cohorts is much lower than from population-based registry counterparts. This difference in EM implies that significant improvements in EM are possible for the general population, and we will explore approaches to improving EM, including supportive care, EM predictive models, and high-volume treatment centers, later in this review.

APL (M3 AML) is a subtype of AML that has a specific balanced translocation t(15;17) that results in the fusion gene *PML-RARA*.[34,35] All-trans retinoic acid is a differentiating therapy that has made APL a highly curable disease. However, APL is associated with life-threatening disseminated intravascular coagulation (DIC) early in the disease course, making EM the main cause of mortality in APL.[36] Clinical trials have reported EM rates of 5% to 10% in APL.[37-39] In comparison, a US population-based study demonstrated that EM is 17.3% in the general population (Table 1).[30] The authors suggested that the higher mortality rates observed in the general population indicate that better recognition of APL as a medical emergency and referral to experienced cancer centers could significantly improve outcomes.

Improvements in Management of Infectious Complications of AML

The findings of reduced EM by Othus et al[15] suggests that improvements in supportive care have been made for patients with AML undergoing induction chemotherapy. Bacterial and fungal infections are major causes of EM in these patients, contributing to up to 71% of deaths within the first week of treatment.[40] As a result, the use of effective, broad-spectrum oral prophylactic antimicrobial therapy has become a routine part of supportive care.[41] Gooley et al[42] first reported decreased hazards of developing bacteremia and invasive mold infections by 39% and 51%, respectively, in hematopoietic stem cell transplant patients as a result of the shift in use of quinolones from cephalosporins and the use of newer mold-active azoles for antimicrobial prophylaxis. Recent meta-analyses and clinical trials have shown that prophylactic treatment with levofloxacin or ciprofloxacin in adult patients with neutropenia is effective and well tolerated, and reduces the incidence of bacteremia and the number of episodes of febrile neutropenia requiring intravenous antibiotic therapy.[43,44] Bucaneve et al[43] conducted a randomized, double-blind, placebo-controlled prospective trial to look at the role of levofloxacin (500 mg per oral route daily) prophylaxis in patients with solid tumors, lymphomas, and acute leukemias at risk for chemotherapy-induced neutropenia. The median age of patients in the antibiotic group was 48 years (range, 18-75 years). The results showed a decrease in the number of febrile episodes (65% in the antibiotic group vs. 85% in the placebo group, $P = .001$) and lower rates of microbiologically documented bacterial infections, with a striking decrease in gram-negative bacteremia resulting from *Escherichia coli*. Overall mortality was 3% in the antibiotic group versus 5% in the placebo group ($P = .15$), and infection-related mortality was 2% versus 4%, respectively ($P = .36$). National Comprehensive Cancer Network (NCCN) guidelines currently recommend the use of a fluoroquinolone, such as ciprofloxacin or

Table 1 Summary of EM in Acute Myeloid Leukemia and APL From Clinical Trials in United States and General Population of Both United States and Sweden

Study	Year	Population Type	Overall EM	EM in Older Adults (>65 Years)
Appelbaum[6]	2006	Clinical trial	12.1% (116/955)	22.6% (79/349)
Juliusson[2]	2009	General Swedish population	19.3% (533/2767)	24.5% (452/1842)
Park[30]	2011	General US APL population	17.3% (242/1400)	24.2% (patients > 55 years)
Othus[15]	2014	Clinical trial	3% in SWOG; 4% in MDA	NA
Hahn[16]	2015	General US population	26.7% (7022/26,272)	35.7% (5444/15,238)

Abbreviations: APL = acute promyelocytic leukemia; EM = early mortality; MDA = MD Anderson Cancer Center; NA = not applicable; SWOG = Southwest Oncology Group.