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Outcomes of Allogeneic Stem Cell Transplantation in Elderly Patients with Acute Myeloid Leukemia: A Systematic Review and Meta-analysis

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A large number of elderly patients with acute myeloid leukemia (AML) are not offered treatments with curative intent, such as allogeneic stem cell transplantation (SCT), because of fears of toxicity and perceived futility of intensive treatment. Therefore, the outcomes of SCT in elderly AML patients remain poorly defined. We performed a meta-analysis of all previous articles up until September 22, 2015 of SCT in AML patients >60 years. The primary endpoints were relapse-free survival (RFS) and overall survival (OS) at 6 months and at 1, 2, and 3 years. A total of 13 studies (749 patients) were included. The pooled estimates and 95% confidence intervals (CI) for RFS at 6 months, 1 year, 2 years, and 3 years were 62% (95% CI, 54% to 69%), 47% (95% CI, 42% to 53%), 44% (95% CI, 33% to 55%), and 35% (95% CI, 26% to 45%), respectively. The corresponding numbers for OS were 73% (95% CI, 66% to 79%), 58% (95% CI, 50% to 65%), 45% (95% CI, 35% to 54%), and 38% (95% CI, 29% to 48%), respectively. We found no evidence of publication bias in our primary endpoints, with the exception of relapse, where there appeared to be a relative lack of small studies with high relapse rates. Sensitivity analysis did not identify an overtly influential study for our primary endpoints, with 1 exception in 2-year RFS analysis. The present analysis argues against significant publication bias and demonstrates consistency among reports despite differences in patient-, disease-, center-, and transplantation-related characteristics. Our results suggest that reduced-intensity SCT is a viable treatment option for elderly AML patients with a 3-year RFS of 35% for those over the age of 60. These results argue against using age per se as the sole criterion against SCT and would help remove some of the barriers that often preclude curative intent treatment. Correct identification of patients who would benefit from SCT can improve outcomes in this frequently undertreated population.

INTRODUCTION

Acute myeloid leukemia (AML) is primarily a disease of the elderly, with a rapidly increasing incidence by age from approximately 50 years, median age at diagnosis of 72 years, and the peak incidence at approximately 80 years of age [1,2]. Outcomes of treatment in AML decline with age, with 2-year overall survival (OS) rates less than 20% in those over the age of 60 [3-5]. Comorbidities and intrinsic biologic factors underlying disease resistance are among causes of poor outcomes in the elderly with AML [4,6]. Nonetheless, 40% to 60% of these patients achieve a complete remission with standard intensive chemotherapy [7]. Even some of the less intensive therapies, such as hypomethylating agents, can result in complete remission rates up to 20% [8-10]. Although most elderly AML patients still succumb to their disease, a recent analysis of the Surveillance, Epidemiology and End Results database demonstrated improved outcomes in older adults (65 to 74 years) with AML over the past 3 decades, with 1-year OS rates of 20% between 1977 and 1986 and 30% between 1997 and 2006 [11]. Reasons for this improvement include better supportive care, infection control, and patient selection.

Allogeneic stem cell transplantation (SCT) is a potentially curative consolidative treatment for patients with AML. While myeloablative (MA) conditioning regimens are associated with unacceptably high toxicity and nonrelapse mortality (NRM) in the elderly [12], reduced-intensity (RI) regimens are both effective and better tolerated, and hence, increasingly used in this population. In patients older than 50

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years of age, RI conditioning is associated with less NRM and similar relapse-free survival (RFS) compared with MA conditioning [13].

A major challenge in the treatment of older adults with AML is our limited ability to identify those who would likely tolerate induction (intensive or less intensive) chemotherapy and/or consolidative SCT. A prevailing perception is that intensive therapy results in unacceptable rates of toxicity in the elderly. As a result, a large number of elderly patients with AML are not offered curative intent treatment because of fears of toxicity, high rates of relapse, and high treatment-related mortality. Between 2000 and 2007, fewer than 40% of AML patients >65 years in the United States received anti-leukemia treatment within 3 months of diagnosis [14]. Similarly, according to recent estimates, only about 6% of AML patients older than 60 in the United States undergo SCT [15]. Publication bias and inconsistency between the results of the available studies are 2 of the usually stated limitations that, although based on little systematically derived evidence, tend to prevent clinicians from applying the available results to more widespread clinical practice.

Because older patients are often excluded from clinical trials, transplantation outcome data in this population are limited, making retrospective reviews and meta-analyses potentially valuable. The purpose of the present study was to determine the outcomes of SCT in elderly AML patients using a systematic review and meta-analysis.

MATERIALS AND METHODS

Data Sources and Searches

We performed this study in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [16]. PRISMA is an evidence-based minimum set of items for reporting in meta-analyses including a 27-item checklist (pertaining to the title, abstract, methods, results, discussion, and funding) and a flow diagram (the flow of information through the different phases of a systematic review). We searched Medline (PubMed) and Embase since their inception for articles written in English published up until September 22, 2015. The Appendix lists the key words used to find studies that included AML patients older than 60 years who underwent SCT. Considering that studies with a focus on patients with myelodysplastic syndrome (MDS) may have included AML patients and reported their outcomes separately, we used MDS-related key words in our search as well.

SELECTION CRITERIA AND DATA EXTRACTION

Duplicates were first removed from the search results. The remaining reports were then screened by scanning titles and abstracts for the following exclusion criteria: reviews or meta-analyses, commentaries, editorials, conference abstracts, reports in languages other than English, no primary endpoints reported, and studies of patients <60 years only. The remaining studies were reviewed in detail. Studies that used both RI and MA conditioning but did not report the outcomes separately were excluded. The corresponding authors of eligible studies with partially missing information were contacted for additional data. Studies were included in data extraction if they reported at least 1 of the 2 primary endpoints. Two authors, A.R. and M.E., independently reviewed the studies, extracted the data, and resolved discrepancies by consensus.

Quality Assessment

All studies were evaluated for quality using a 2-item scoring system. The items were specific conditioning regimen(s) and median age. For each item, studies received a score of 1 if the information was provided in the report and 0 otherwise. The total quality score (range, 0 to 2) was calculated by adding the scores for individual items. A higher total score indicated a higher quality study. These scores were not a basis for inclusion or exclusion of studies.

Statistical Analysis

The primary endpoints were OS and RFS at 6 months, 1 year, 2 years, and 3 years, measured from the time of SCT. OS was defined as time to death or last follow-up, if alive. Secondary endpoints were the cumulative incidence of relapse (CIR) and NRM (death unrelated to relapse). Study heterogeneity was assessed using the Cochran Q test and quantified using the I^2 statistic. A random effects model was first used to calculate pooled proportions with 95% confidence intervals (95% CI) in proportion meta-analysis [17]. In analyses with no significant heterogeneity, the model was then changed to fixed effects. Publication bias was assessed using funnel plots and Egger test. Meta-regression (1 covariate at a time) was used to determine the effect of potential variables (median age, maximum age, accrual initiation year, gender, cytogenetic risk, and donor type) on outcomes. Regression was performed only when the number of eligible studies was larger than 5. Two-sample independent student's *t*-test was used to evaluate the effect of study scale (single-center versus multicenter). Finally, sensitivity analysis was performed by removing individual studies and repeating the analysis to determine the influence of each study on the pooled estimate. A study was considered overtly influential if the change in the pooled estimate for proportion after removing the study was >10%. STATA 13 (College Station, TX) was used for analysis. *P* values < .05 were considered statistically significant.

RESULTS

A total of 14 reports were studied in detail (Figure 1, Table 1) [12,18-29]. All but 2 studies were retrospective and 6 were multicenter. All studies were single-arm studies; 13 used RI and 1 used MA conditioning. Because only 1 study used MA conditioning [12], this study was not analyzed. The included studies had a total of 749 eligible patients. The sample size ranged between 6 and 195. The proportion of patients with poor-risk cytogenetics ranged between 6% and 29%. Eleven studies scored 2, and 3 studies scored 1.

The pooled estimates for RFS at 6 months, 1 year, 2 years, and 3 years were 62% (95% CI, 54% to 69%), 47% (95% CI, 42% to 53%), 44% (95% CI, 33% to 55%), and 35% (95% CI, 26% to 45%), respectively (Figure 2). The corresponding numbers for OS were 73% (95% CI, 66% to 79%), 58% (95% CI, 50% to 65%), 45% (95% CI, 35% to 54%), and 38% (95% CI, 29% to 48%), respectively (Figure 3). The pooled estimates for CIR at 6 months, 1 year, 2 years, and 3 years were 33% (95% CI, 25% to 42%), 39% (95% CI, 31% to 48%), 39% (95% CI, 34% to 44%), and 39% (95% CI, 30% to 48%), respectively (Figure S1). The corresponding numbers for NRM were 13% (95% CI, 4% to 25%), 26% (95% CI, 15% to 39%), 29% (95% CI, 20% to 40%), and 40% (95% CI, 25% to 57%), respectively (Figure S2). Figure 4 shows reconstructed curves for outcomes at different time points.

There was no evidence of statistical heterogeneity among studies in 2-year CIR (chi-square, 2.6; I^2, 0), 6-month RFS (chi-square, .1; I^2, 0), 1-year RFS (chi-square, 2.1; I^2, 0), 6-month OS (chi-square, 1.6; I^2, 0), and 1-year OS (chi-square, 5.4; I^2, 6.9%). In contrast, a significant proportion of interstudy variation in 3-year CIR (chi-square, 8.9; I^2, 54.9%), 6-month NRM (chi-square, 6.5; I^2, 53.5%), 1-year NRM (chi-square, 15.5; I^2, 74.1%), 2-year NRM (chi-square, 32.1; I^2, 78.2%), 3-year NRM (chi-square, 24.3; I^2, 83.5%),