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Clinical Research

Effect of Postremission Therapy before Reduced-Intensity Conditioning Allogeneic Transplantation for Acute Myeloid Leukemia in First Complete Remission

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The impact of pretransplant (hematopoietic cell transplantation [HCT]) cytarabine consolidation therapy on post-HCT outcomes has yet to be evaluated after reduced-intensity or nonmyeloablative conditioning. We analyzed 604 adults with acute myeloid leukemia in first complete remission (CR1) reported to the Center for International Blood and Marrow Transplant Research who received a reduced-intensity or nonmyeloablative conditioning HCT from an HLA-identical sibling, HLA-matched unrelated donor, or umbilical cord blood donor from 2000 to 2010. We compared transplant outcomes based on exposure to cytarabine postremission

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consolidation. Three-year survival rates were 36% (95% confidence interval [CI], 29% to 43%) in the no consolidation arm and 42% (95% CI, 37% to 47%) in the cytarabine consolidation arm ($P = .16$). Disease-free survival was 34% (95% CI, 27% to 41%) and 41% (95% CI, 35% to 46%; $P = .15$), respectively. Three-year cumulative incidences of relapse were 37% (95% CI, 30% to 44%) and 38% (95% CI, 33% to 43%), respectively ($P = .80$). Multivariate regression confirmed no effect of consolidation on relapse, disease-free survival, and survival. Before reduced-intensity or nonmyeloablative conditioning HCT, these data suggest pre-HCT consolidation cytarabine does not significantly alter outcomes and support prompt transition to transplant as soon as morphologic CR1 is attained. If HCT is delayed while identifying a donor, our data suggest that consolidation does not increase transplant treatment-related mortality and is reasonable if required.

INTRODUCTION

Decision-making regarding type of consolidation therapy after first complete remission (CR1) for acute myeloid leukemia (AML) depends on many patient- and disease-related variables. Postremission consolidation cytarabine chemotherapy can potentially cure a subset of AML patients, especially those with core binding factor leukemias [1-3]. However, a meta-analysis has suggested a survival benefit for a broader application of allografts for all intermediate and high risk AML patients in CR1, excluding only those with good risk cytogenetic or molecular features [4].

When an allograft is planned in a patient with AML in CR1, an abbreviated course of cytarabine consolidation therapy is often offered before hematopoietic cell transplantation (HCT) while a donor is being identified. Despite this common practice, the impact of pretransplant consolidation chemotherapy on post-HCT outcomes for AML CR1 patients has not been prospectively evaluated. This question has been retrospectively addressed by prior Center for International Blood and Marrow Transplant Research (CIBMTR) and European Group for Blood and Marrow Transplantation analyses with myeloablative (MA) conditioning. Pretransplant consolidation therapy did not alter survival or relapse and did not increase transplant-related mortality (TRM) [5,6]. The influence of pretransplant cytarabine consolidation chemotherapy in the setting of reduced-intensity conditioning (RIC)/non-MA (NMA) HCT for this patient population is uncertain. Prior retrospective analyses comparing outcomes after MA or RIC/NMA conditioning suggest a higher rate of relapse after RIC/NMA HCT but less TRM and thus similar survivals, even in older populations receiving RIC HCT [7-9]. These data would theoretically lead to the hypothesis that pre-HCT chemotherapy might reduce relapse risk after RIC all-HCT. Most recent retrospective and prospective publications, however, have challenged this earlier supposition, showing relatively similar relapse and TRM, regardless of conditioning intensity [10-13].

In the context of expanding use of RIC/NMA HCT, a setting where more stringent disease control may be desirable, the effectiveness of pre-HCT consolidation chemotherapy is largely unknown. A retrospective analysis from the University of Minnesota compared the outcomes of 60 AML patients in CR1 undergoing the same RIC HCT from 2001 to 2008 based on exposure to pre-HCT consolidation chemotherapy [14]. The investigators reported similar relapse and survival in subjects who did or did not receive pre-HCT consolidation [14]. To define the value of pre-RIC/NMA HCT consolidation chemotherapy for AML in CR1, we addressed this question in a large dataset from the CIBMTR.

METHODS

Data Source

The CIBMTR includes a voluntary working group of more than 450 transplantation centers worldwide that contribute detailed data on consecutive allogeneic and autologous HCT to a Statistical Center at the Medical College of Wisconsin in Milwaukee and the National Marrow Donor Program Coordinating Center in Minneapolis. Participating centers are required to report all transplants consecutively; patients are followed longitudinally, and compliance is monitored by on-site audits. Computerized checks for discrepancies, physicians' review of submitted data, and on-site audits of participating centers ensure data quality. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected Health Information used in the performance of such research is collected and maintained in CIBMTR's capacity as a Public Health Authority under the HIPAA Privacy Rule.

Patient Selection

All adult patients reported to the CIBMTR who received a RIC or NMA conditioning HCT for AML in CR1 from either an HLA-identical sibling, unrelated donor (URD), or umbilical cord blood (UCB) donor from 2000 to 2010 were included in this analysis. Patients with French American British (FAB) subtype M3 were excluded. The very few patients with favorable risk cytogenetics (n = 8) were also excluded.

A total of 604 patients was identified from 165 centers. Patients were initially divided into 3 cohorts for analysis: (1) no postremission therapy before transplant, (2) standard-dose cytarabine consolidation therapy (defined as $\leq$1 g/m^2/day on earlier CIBMTR data submission forms [pre-2008] or $\leq$2 g/m^2/day on current forms), or (3) high-dose cytarabine consolidation therapy (defined as $>$1 g/m^2/day on earlier forms or $>$2 g/m^2/day on current forms). However, because no difference was seen between lower and higher dose consolidation cohorts, the final analysis compared no cytarabine consolidation versus any dose of cytarabine consolidation.

Patients included in the study cohort received a maximum of 2 cycles of induction therapy to obtain CR1 status. CIBMTR classifications of URD matching were used to define well-matched, partially matched, or mismatched categories [15]. Preparative regimens were classified as either RIC or NMA by established CIBMTR functional definitions. RIC included any regimen with either (1) 500 cGy or less of total body irradiation as a single fraction or 800 cGy or less if fractionated (2) $<$9 mg/kg busulfan oral (or intravenous equivalent), (3) $<$140 mg/m2 melphalan, (4) $<$10 mg/kg thiotepa, or (5) BEAM regimen (carmustine, etoposide, cytarabine, and melphalan) [16,17]. All other regimens were classified as NMA conditioning according to Champlin et al. [18] where prompt hematopoietic recovery could reasonably be expected without a transplant and would produce mixed chimerism after engraftment post-transplant. Based on these classifications, the most common RIC regimens included (1) fludarabine + busulfan, (2) fludarabine + melphalan, (3) fludarabine + cyclophosphamide, and (4) other. NMA regimens included fludarabine + low-dose total body irradiation ($\leq$200 cGy) and fludarabine + antithymocyte globulin.

Study Endpoints

The primary endpoint was overall survival (OS) in those with or without pre-HCT consolidation chemotherapy. Secondary endpoints included hematopoietic recovery, occurrence of acute and chronic graft-versus-host disease (GVHD), TRM, incidence of relapse, and disease-free survival (DFS). OS was defined as time to death from any cause with surviving patients censored at time of last contact. Hematopoietic recovery was defined as time to absolute neutrophil count $\geq$ 500 neutrophils/μL sustained for 3 consecutive days. Criteria for acute and chronic GVHD were based on consensus criteria as previously defined [19,20]. TRM was defined as any death in the first 28 days post-transplant or any death after day 28 without recurrent leukemia. Relapse was defined as hematologic evidence of disease recurrence with those surviving without relapse censored at the date of last contact and using death in remission as the competing hazard. DFS was defined as survival without death or relapse with those who survived without recurrence or persistent disease censored at the date of last contact.