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Fludarabine-Busulfan Reduced-Intensity Conditioning in Comparison with Fludarabine-Melphalan Is Associated with Increased Relapse Risk In Spite of Pharmacokinetic Dosing

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Fludarabine with busulfan (FB) and fludarabine with melphalan (FM) are commonly used reduced-intensity conditioning (RIC) regimens. Pharmacokinetic dosing of busulfan (Bu) is frequently done for myeloablative conditioning, but evidence for its use is limited in RIC transplants. We compared transplant outcomes of FB versus FM using i.v. Bu targeted to the area under the curve (AUC). A total of 134 RIC transplants (47 FB and 87 FM) for acute myelogenous leukemia and myelodysplastic syndrome were identified, and median follow-up of the cohort was 40 months (range, 0 to 63.3). A significantly higher 2-year cumulative incidence of relapse (CIR) was associated with FB versus FM at 35.6% versus 17.3%, respectively ($P = .0058$). Furthermore, 2-year progression-free survival rates were higher for FM versus FB at 60.5% versus 48.7%, respectively ($P = .04$). However, 2-year rates of nonrelapse mortality (NRM) and overall survival (OS) were similar. The need for dose adjustment based on AUC did not alter relapse risk or NRM. Patients with Karnofsky performance status ≥ 90 who received FM had a 2-year OS rate of 74.8% versus 48.3% for FB ($P = .03$). FB use remained prognostic for relapse in multivariable analysis (hazard ratio, 2.75; 95% confidence interval, 1.28 to 5.89; $P = .0097$). In summary, in spite of AUC-directed dosing, FB compared with FM was associated with a significantly higher CIR.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HCT) is a potentially curative therapy for hematologic malignancies. Traditionally, standard myeloablative conditioning regimens limit the utility of this therapy to medically fit patients because of prohibitive toxicity in the elderly and those with multiple prior therapies or comorbidities. The advent of reduced-intensity conditioning (RIC) has expanded access of HCT to many patients who were previously ineligible [1-3]. The specifics of what constitutes a RIC protocol is subject to much debate; however, based on available evidence and expert opinion, the Center for International Blood and Marrow Transplant Research has used certain criteria to define properties of RIC [4]. Although multiple RIC regimens have been developed, there is a paucity of prospective comparative data and the chosen conditioning relies mostly on the preferences and experience of the transplant center. Fludarabine with intermediate-dose busulfan (FB) and fludarabine with intermediate-dose melphalan (FM) are 2 of the most commonly used RIC protocols for allogeneic transplantation. Along the spectrum of conditioning regimens, both FM and FB are considered “equivalent” in terms of their myelosuppressive and immune-suppressive properties [5].

Two prior retrospective studies have compared these regimens. Shimoni et al. [6] investigated a cohort of 151 patients with various hematologic malignancies who received FB (n = 72) or FM (n = 79). A higher proportion of

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patients receiving FM had lymphoid malignancies, including myeloma, and the converse for FB where myeloid disorders were more prevalent. The authors reported that FM was more myelosuppressive and associated with higher rates of nonrelapse mortality (NRM) but also exhibited more potent disease control with lower cumulative incidence of relapse (CIR). Overall survival (OS) was better with FB for patients in remission before allogeneic HCT but was equivalent between both regimens for patients transplanted with active disease.

More recently, a report from the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation studied a homogenous group of 394 patients with acute myeloid leukemia (AML) who received grafts from identical siblings using FB or FM-RIC [7]. The authors again showed that FM is associated with lower incidence of relapse (IR), but OS was comparable with FB due to higher NRM in the FM group. Importantly, approximately two thirds of the FB cohort received oral busulfan (Bu), and the efficacy of such administration is associated with unpredictable bioavailability, leading to higher risk of untoward toxicity or suboptimal antileukemic activity [8,9]. Furthermore, because of first-pass metabolism in the liver, oral administration of Bu seems to be associated with an elevated risk of veno-occlusive disease and sinusoidal obstructive syndrome [10-14].

An intravenous preparation of Bu was developed that has more predictable pharmacokinetic consistency and safety, and it has become a favored form of administration [15,16]. Traditionally, 4-times-daily dosing of Bu was used; however, a more convenient once-daily dosing has demonstrated equivalent efficacy in multiple studies [9,17]. Systemic Bu exposure measured by a steady-state concentration or area under the curve (AUC) plasma concentration correlates with risk of toxicity, graft rejection, and relapse, reflecting an association between exposure and outcome. This association has resulted in the hypothesis that pharmacokinetic-based dose monitoring and adjustment may potentially improve transplant outcomes [18,19]. However, the bulk of available literature reflects full-intensity dosing of Bu, and little is known regarding whether drug monitoring of RIC dosing is necessary.

In light of this, our aim was to compare HCT outcomes in a population of patients with AML and myelodysplastic syndrome (MDS) conditioned with 2 very commonly used RIC regimens, FB and FM, where Bu was administered intravenously to all patients. Furthermore, a secondary aim was to study the impact of AUC dose monitoring and subsequent dose adjustment, if necessary.

METHODS

Patient Selection

After institutional review board approval, adult patients ≥18 years of age with AML or MDS receiving RIC-HCT from 2008 to 2014 were retrospectively identified using the Mayo Clinic Rochester electronic database. The selection criteria included patients receiving RIC-HCT with FB or FM as conditioning regimen from related or unrelated donor sources. All patients were considered not to be candidates for full-intensity conditioning at the discretion of the transplant physician. Exclusion criteria included patients who received a cord blood stem cell source, second transplant, T cell depletion, and haploidentical transplant. All patients received i.v. Bu with targeted dose to the AUC. Data were collected retrospectively from patients' electronic medical records and were stratified per the conditioning regimen. Cytogenetic data at the time of diagnosis were available in 134 patients (100%) and were stratified as previously described for AML and MDS patients [20,21]. At the time of transplant, the Karnofsky performance status (KPS) and HCT-specific comorbidity index was calculated for each patient as previously reported [22].

Treatment Protocol

FM was the sole conditioning regimen used until July 2011, when FB with AUC monitoring was introduced and became the dominant regimen by 2013. Between 2011 and 2013 the choice of regimen was at the discretion of the treating physician. The conditioning regimen for FM consisted of fludarabine 25 mg/m^2 (days −6 to −2) for 5 days and melphalan 70 mg/m^2 (days −3 and −2) for 2 days [23]. FB consisted of fludarabine 30 mg/m^2 (days −7 to −2) for 6 days and i.v. Bu .8 mg/kg of actual or ideal body weight, whichever is lower, given every 6 hours (days −4 to −2) for a total of 10 doses, with dose adjustment based on the first-dose AUC, for subsequent doses if necessary [24]. Phenytoin was used for seizure prophylaxis for Bu-containing regimens. Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine for sibling donor transplant or tacrolimus for unrelated donor transplant in combination with methotrexate.

Pharmacokinetic Monitoring

Bu was administered over 2 hours every 6 hours i.v. for a total of 10 doses. AUC was measured before infusion and then 1, 2, and 4 hours after completion of the 2-hour infusion. Each specimen was drawn at the indicated time interval, and the exact draw time was labeled on the tube. The infusion start and termination time were documented in addition to the patient's dose, body weight, and age. Blood was drawn in a sodium heparin–containing tube and then sent to the central processing laboratory on ice. There it was spun, and 1 mL of sodium heparin plasma aliquot was frozen in a plastic vial and sent for analysis. The Bu level at 4 time intervals was used to construct a 6-hour AUC. The optimal AUC level considered was 1100 (μM/L) (min) with the therapeutic range between 900 and 1500 (μM/L) (min) [25-27].

Definitions and Transplant-Related Outcomes

OS was calculated from the date of transplant until the date of death of any cause or last documented follow-up date. Progression-free survival (PFS) was calculated from the time of transplant until death or relapse. CIR was calculated from the date of transplant until relapse or date of last follow-up. Cumulative incidence of NRM was calculated from the date of transplant until death of any cause without evidence of disease relapse. Acute and chronic GVHD were graded according to standard criteria [28,29]. Neutrophil engraftment was defined as an absolute neutrophil count of .5 × 10^9/L or higher for 3 consecutive days. Platelet engraftment was defined as a platelet count higher than 20 × 10^9/L for 7 consecutive days without transfusion support. Monosomal karyotype was defined as the presence of at least 2 autosomal monosomies or 1 autosomal monosomy associated with another structural abnormality. Secondary disease refers to acute leukemia arising from an antecedent hematologic disorder (such as MDS, myeloproliferative neoplasm or myelodysplastic/myeloproliferative overlap syndrome) or therapy related to exposure to cytotoxic agents or ionizing radiation.

Statistical Analysis

Baseline patient-, disease-, and treatment-related variables were stratified per conditioning regimen and reported using descriptive statistics (counts, medians, and percentages). Categorical and continuous variables were compared using Pearson's chi-squared and Wilcoxon/Kruskal-Wallis tests, respectively. Probability of OS was computed using the Kaplan-Meier method. Group comparisons were made using the log-rank test. Time to event was calculated from the date of transplant until the event or point of last clinical encounter, which in the latter case the event was censored. Cumulative incidence was computed as competing events using Grey's model, considering death as a competing event for relapse and acute or chronic GVHD and relapse as a competing event for NRM. Univariable and multivariable analyses were performed using Cox proportional hazard regression modeling. Any variable with a $P \leq .15$ was incorporated into the multivariable model. Given baseline differences among the cohorts for age at HCT and cytomegalovirus serologic status, those variables were incorporated into the multivariable model. Statistical analyses were performed using JMP Pro Version 11 (SAS Institute, Cary, NC) software and EZR on R commander version 1.28 [30].

RESULTS

Baseline Characteristics of FB versus FM Cohorts

During the study period, 134 consecutive patients were identified who met the eligibility criteria. Eighty-seven patients (65%) received FM and 47 (35%) received FB; all patients received i.v. Bu. Baseline patient-, disease-, and transplant-related characteristics stratified by conditioning regimen are shown in Table 1. Median age in the FM group