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Dose Escalation of Total Marrow Irradiation in High-Risk Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplantation

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Patients with refractory leukemia or minimal residual disease (MRD) at transplantation are at increased risk of relapse. Augmentation of irradiation, especially to sites of disease (ie, bone marrow) is one potential strategy for overcoming this risk. We studied the feasibility of radiation dose escalation in high-risk patients using total marrow irradiation (TMI) in a phase I dose-escalation trial. Four pediatric and 8 adult patients received conditioning with cyclophosphamide and fludarabine in conjunction with image-guided radiation to the bone marrow at 15 Gy and 18 Gy (in 3-Gy fractions), while maintaining the total body irradiation (TBI) dose to the vital organs (lungs, hearts, eyes, liver, and kidneys) at <13.2 Gy. The biologically effective dose of TMI delivered to the bone marrow was increased by 62% at 15 Gy and by 96% at 18 Gy compared with standard TBI. Although excessive dose-limiting toxicity, defined by graft failure or excessive specific organ toxicity, was not encountered, 3 of 6 patients experienced treatment-related mortality at 18 Gy. Thus, we halted enrollment at this dose level and treated an additional 4 patients at 15 Gy. The 1- year overall survival was 42% (95% confidence interval [CI], 15%-67%) and disease-free survival was 22% (95% CI, 4%-49%). The rate of relapse was 36% (95% CI, 10%-62%), and nonrelapse mortality was 42% (95% CI, 14%-70%). This study shows that TMI dose escalation to 15 Gy is feasible with acceptable toxicity in pediatric and adult patients with high-risk leukemia undergoing umbilical cord blood and sibling donor transplantation.

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INTRODUCTION

Allogeneic hematopoietic cell transplantation (allo-HCT) is potentially curative for a variety of malignant disorders. Allo-HCT is typically performed when patients are in remission, and most studies support this practice because of the poor outcomes of transplantations performed during periods of relapse. Using Center for International Blood and Marrow Transplant Research registry data, Duval et al. [1] found that patients who underwent transplantation while in relapse had a 3-year event-free survival of 16% for acute lymphoblastic leukemia and 19% for acute myelogenous leukemia. Even when allo-HCT is performed in remission, relapse rates vary widely, ranging from 25% to 40%, depending on such factors as the primary disease, number of previous remissions, detectable minimal residual disease (MRD), and intensity of the conditioning regimen.

Over the last 5 to 10 years, advances in quantitative PCR and multiparameter flow cytometry are allowing for the detection of small quantities of MRD in patients who are in morphological remission. This technology has led to a growing appreciation of the variation in leukemic burden before allo-HCT in patients who are in remission. Some studies have shown a strong relationship between pretransplantation MRD and relapse [2,3]. At present, how to reduce the risk of relapse in patients with active leukemia or detectable pretransplantation MRD is unclear [4]. Providing additional chemotherapy before transplantation to reduce MRD also

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might be possible, and additional pretransplantation chemotherapy carries a risk of leukemic progression and/or end-organ toxicity, which may preclude transplantation or increase the risk of treatment-related mortality (TRM).

Radiation is an effective component of the transplantation conditioning regimen, for both its immunosuppressive properties and its direct antileukemia activity. Although leukemia cells from heavily pretreated patients are likely to develop chemoresistance, whether this correlates with radiation resistance is less clear. Considering that most patients with leukemia are radiation-naïve, the use of radiation is logical, and it is widely used in pretransplantation conditioning regimens, especially for patients with lymphoid diseases. One potential method to increase leukemia cell kill might be to augment the radiation dose in the conditioning regimen, which in turn would be expected to enhance leukemia control [5]. The higher biological effective dose (BED) associated with total body irradiation (TBI) doses of >13 Gy was significantly correlated with reduced leukemia relapse and/or better disease-free survival (DFS) [6,7]. However, due to the inherent lack of precision of TBI and the sensitivity of vital organs, higher irradiation doses also risk injury to healthy tissues that are not commonly thought to be the main sites of leukemic involvement. Proof of both the benefit and the toxicity of higher-dose TBI was provided by Clift et al. [8-10], who randomized patients to receive either standard-dose (12 Gy) or increased-dose TBI (15.75 Gy) TBI. Although the higher radiation dose resulted in reduced relapse, it also increased TRM, resulting in equivalent survival in the 2 groups.

This finding suggests that TBI is limited by the toxicity to vital organs, especially the lungs, liver, eyes, heart, and kidneys [11-14]. Although these organs may be involved in the leukemic process, the bone marrow and lymphoid tissue are believed to be the major sites of residual disease in patients needing allo-HCT. With the introduction of helical tomotherapy, a new potential exists to conform the radiation dose to very specific areas of the body, such as the bone marrow. In a previous preclinical study [15], using a nonhuman phantom, we showed that helical tomotherapy is accurate and that conformal irradiation can be directed to the bone marrow while minimizing the radiation dose to vital organs. In that preclinical study of total marrow irradiation (TMI), the average irradiation doses to the lungs, heart, eyes, liver, and kidneys were reduced by 40% to 60% compared to conventional TBI. Thus, we hypothesized that it is possible to use TMI to escalate the irradiation dose to the marrow-containing spaces (ie, sites of disease) while maintaining the radiation to vital organs at an acceptable limit (ie, <13.2 Gy). We tested this hypothesis in a cohort of high-risk patients with leukemia undergoing myeloablative allo-HCT who were refractory to chemotherapy or had pretransplantation MRD.

PATIENTS AND METHODS

Patient Eligibility and Donor Selection

Patients were eligible if they had adequate performance status (Karnofsky Performance Status >80% for patients age >16 years or Lansky Play Score >50 for younger patients) and acceptable organ function (glomerular filtration rate >60 mL/min/1.73 m^2, bilirubin and alanine aminotransferase <5 times the upper limit of normal, diffusing capacity of the lung for carbon monoxide corrected for hemoglobin >50% of normal, and left ventricular ejection fraction ≥45% by echocardiography or multiple-gated acquisition scan). Patients were eligible who did not achieve remission with standard induction and salvage chemotherapy or who had evidence of pretransplantation MRD by 8-color flow cytometry, fluorescein in situ hybridization, or cytogenetics. Patients with evidence of pregnancy, HIV infection, or uncontrolled serious infection within the previous 3 months were excluded from this trial. Allogeneic donors were closely HLA-matched umbilical cord blood (UCB) or related donors. This study was approved by the University of Minnesota's Institutional Review Board and was registered as NCT00686556 on clinicaltrials.gov.

Dose Escalation and Treatment

The treatment schema is shown in Figure 1A. All patients received fludarabine (25 mg/m^2 for 3 consecutive days) and cyclophosphamide (60 mg/kg/day i.v. for 2 days), followed by dose-escalated TMI. Details of the TMI technique have been described previously [16-18]. In brief, the patient was immobilized using the Body Pro-Lok system (CIVCO, Orange City, IA) to ensure consistent positioning during treatment. For pretreatment planning, images were acquired using conventional computed tomography (CT) with a kilovoltage CT scanner (Brilliance CT Big Bore; Philips Healthcare, Cleveland, OH). The bony anatomy was contoured in 4 regions——bones of the skull, thoracic bones, upper extremities, and pelvis——and used to calculate the clinical target volume. To account for day-to-day variability during preirradiation patient positioning within the tomotherapy device and positional movement of breathing during irradiation, a planning target volume was generated with 5- to 15-mm margins around the clinical target volume, depending on the skeletal site. The margins were set by taking into consideration the anatomic region, variations in the precise localization of individual regions before each TMI treatment delivery, using the course mode (lower resolution) of megavoltage CT (MVCT) imaging to scan the whole body. The resulting images and contours were then transferred to the Tomotherapy HiArt Planning Station (Tomotherapy, Madison, WI).

An optimal treatment plan was created to deliver the prescribed dose (3 Gy/fraction in 5 or 6 fractions) to the planning target volume and the reduced radiation dose to vital organs, as described previously [18]. The rationale for selecting 3 Gy/fraction was derived from our previous study using TMI simulation, where we considered the lungs the single most vital organ for toxicity [17]. In that study, the achievable mean lung dose was ~50% to 55% of the prescribed bone marrow dose. Thus, to keep the mean lung dose ≤1.65 Gy/fraction (equivalent to the mean lung dose for conventional TBI), we could deliver 3 Gy/fraction to the bone marrow. In addition, in our dose-escalation strategy, the total lung dose never exceeded the standard TBI dose of 13.2 Gy. Dose volume histograms were calculated for the target (ie, bone

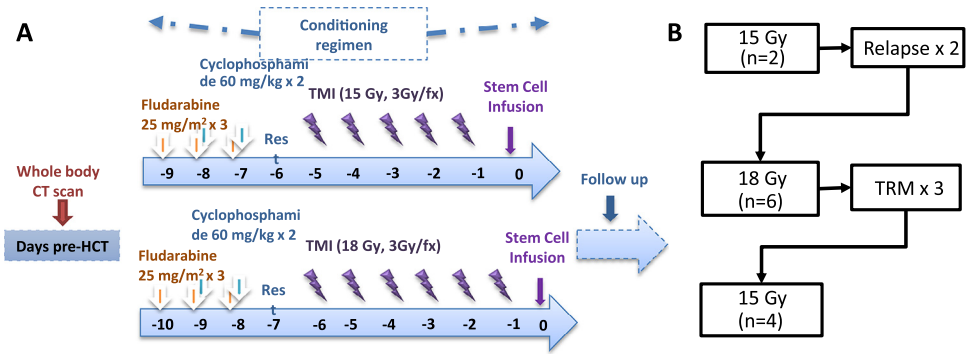

Figure 1. Schematic representation of the dose escalation regimen. (A) All patients received fludarabine and cyclophosphamide and escalating doses of TMI. (B) Steps of dose escalation. Nine of 12 patients received UCB grafts, and the other 3 received peripheral blood stem cell grafts.

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