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# Incidence of Viral and Fungal Infections following Busulfan-Based Reduced-Intensity versus Myeloablative Conditioning in Pediatric Allogeneic Stem Cell Transplantation Recipients

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Reductions in the duration and nadir of neutropenia have translated into a significant decrease in bacteremia in adult recipients of allogeneic stem cell transplantation (allo-SCT) with reduced-intensity conditioning (RIC) during the first 30 days after transplantation. It remains to be determined whether RIC allo-SCT also will result in a decrease in systemic viral infections (SVIs) and invasive fungal infections (IFIs), which are more dependent on alterations in cellular immunity. We compared the incidence of SVIs and IFIs in children receiving busulfan-based RIC allo-SCT and in children receiving myeloablative conditioning (MAC) allo-SCT for various malignant and nonmalignant diseases. Allo-SCT recipients at risk for cytomegalovirus (CMV) received ganciclovir/foscarnet, and most of the patients received antifungal prophylaxis with liposomal amphotericin B until day +100. Eighty-six patients (median age, 7.5 years; 70% with malignant disease, 30% with nonmalignant disease; 80% average risk, 20% poor risk) were evaluated. The probability of developing grade II-IV acute graft-versus-host disease (aGVHD) was 29.1% (95% confidence interval [CI]=16.7%-41.6%) in RIC allo-SCT versus 40.3% (95% CI=23.9%-56.6%) in MAC allo-SCT (*P*=.23), and that of chronic GVHD (cGVHD) was 28.9% (95% CI=14.7%-43.0%) in RIC allo-SCT versus 28.4% (95% CI=10.5%-46.3%) in MAC allo-SCT (*P*=.73). The overall probability of developing an SVI was 58%, and that of developing an IFI was 15%. These probabilities did not differ significantly by conditioning intensity. In a multivariate Cox regression model, the following were identified as independent risk factors for invasive fungal infection: older age (hazard ratio [HR]=1.3; 95% CI=1.1-1.6; *P*=< .01), poor risk status (HR=6.5; 95% CI =1.1-37.4; *P*=.03), and CMV-positive recipient (high vs low CMV risk group, HR=26.7; 95% CI=3.4-210.8; *P*=< .01). Overall infection-related mortality was only 1.1% (1/86) for SVIs and 2.3% (2/86) for IFIs. Our data indicate that RIC allo-SCT does not carry a lower risk of SVIs and IFIs than MAC allo-SCT in pediatric recipients.

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## INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-SCT) as a treatment option for hematologic malignancies has long been based on the assumption that myeloablative (MA) doses of cytotoxic therapy are required for both disease eradication and host immunosuppression. But the last decade has seen a paradigm shift toward the curative potential of a graft-versus-leukemia (GVL) or graft-versus-tumor (GVT) effect [1]. The concept behind reduced-intensity conditioning (RIC) allo-SCT is that instead of eradicating tumors through intensive/toxic chemoradiation, tumor eradication is done using the SCT donor's immune cells, relying on allogeneic GVT effects [2]. In patients with nonmalignant disease, the aim of RIC allo-SCT is to create an immunologic platform of host and donor

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tolerance using pretransplantation and posttransplantation immunosuppression.

Data on RIC allo-SCT in pediatric recipients are limited [3,4]. We previously demonstrated the feasibility and safety of the RIC allo-SCT approach in children with malignant and nonmalignant diseases [5,6]. We also demonstrated the safety of RIC allo-SCT and consolidation with gemtuzumab ozagamicin in children with average-risk acute myelogenous leukemia (AML) [7].

Following myeloablative conditioning (MAC) allo-SCT, patients experience a period of profound neutropenia, severe mucositis, and immunodeficiency that can lead to serious infectious complications that may result in significant morbidity and mortality. Theoretically, RIC allo-SCT could carry a lower risk of opportunistic infections. The potential mechanism(s) that may be responsible for this hypothetical reduced infectious morbidity following RIC allo-SCT includes shorter duration of severe neutropenia, lower grade of mucositis, enhanced immune reconstitution, decreased rate of severe acute graft-versus-host disease (aGVHD), and less use of immunosuppression compared with MAC allo-SCT [8,9]. Junghanss et al. [10] reported a significantly reduced risk of bacterial infection during the first 100 days posttransplantation in adult recipients of RIC allo-SCT. But, because of intense pretransplantation and/or posttransplantation immunosuppression, patients receiving RIC regimens actually may be at greater risk for systemic viral infections (SVIs) and invasive fungal infections (IFIs). Identified risk factors for developing SVIs after RIC allo-SCT include lymphopenia, cytomegalovirus (CMV), serologic status of the donor and recipient, in vivo T cell depletion using antithymocyte globulin (ATG) or alemtuzumab, and ex vivo T cell depletion [11,12].

Adenovirus (ADV) and CMV are serious causes of morbidity and mortality in patients undergoing allo-SCT. CMV infection is one of the most devastating infectious complications associated with allo-SCT. CMV reactivation occurs in 60%-80% of allo-SCT recipients who are CMV-seropositive and/or have a seropositive donor and do not receive CMV prophylaxis and/or preemptive therapy [13]. The rate of ADV infection in allo-SCT recipients is 5%-27%, and mortality ranges from 8% to 54%. The mortality rate is higher in patients with ADV pneumonia (73%) and disseminated disease (61%) [14]. The rate of ADV infection is 4%-6% in adult allo-SCT recipients, but as high as 47% in pediatric allo-SCT recipients [15].

IFI is another leading cause of infectious mortality following allo-SCT (10%-20%) [16]. The incidence of IFIs has increased from 5.7% to 11.2% over the last decade [17]. Risk factors for developing an IFI include prolonged neutropenia, unrelated or mismatched donor source, and aGVHD or chronic GVHD (cGVHD) and its treatment. Adult RIC allo-SCT and MAC allo-SCT recipients have equivalent risks for aspergillosis; however, there was a trend toward increased 1-year survival in RIC allo-SCT recipients following invasive aspergillosis [18].

There have been a few prospective and retrospective studies in adults regarding the incidence and outcome of SVIs and IFIs following RIC allo-SCT [10-12]. Some of those studies have suggested that RIC allo-SCT is associated with increased risk of CMV, Epstein-Barr virus (EBV), ADV, and IFIs [14-18]. Children undergoing allo-SCT may be at greater risk for primary viral infections; however, there is a paucity of data on SVIs and IFIs in children following RIC and MAC allo-SCT. In the present study, we compared the incidence and risk factors for SVIs and IFIs following busulfan-based RIC allo-SCT versus MAC allo-SCT.

## PATIENTS AND METHODS

### Patients

Patients included consecutive children and adolescents who underwent busulfan (Bu)-based RIC allo-SCT at the Morgan Stanley Children's Hospital of New York-Presbyterian, between January 2001 and December 2007. Indications for transplantation included various malignant and nonmalignant conditions. Allogeneic stem cell sources included bone marrow (BM), peripheral blood stem cells (PBSCs), and umbilical cord blood (UCB). Poor-risk malignant patients were defined as those with chemoresistant malignant disease, in third complete remission (CR3) or greater, induction failure, progressive disease, and/or receiving a second allograft. All other patients with malignant and nonmalignant diseases were defined as average risk. All patients were on clinical protocols for allo-SCT approved by the Institutional Review Board at Columbia University Medical Center, and all research protocols were in compliance with the Declaration of Helsinki.

### Conditioning Regimens

The conditioning regimens were protocol-driven and disease-specific. Patients with comorbid features before undergoing allo-SCT were prioritized for RIC regimens; prioritization of the remaining patients was protocol-driven and disease-specific. All patients without comorbid features were offered MAC. The RIC arm included patients who received Bu (6.4-8 mg/kg), fludarabine (Flu; 150-180 mg/m$^2$) ± rabbit antithymocyte globulin (ATG; 8 mg/kg) or Bu (12.8-16 mg/kg), and Flu (150-180 mg/m$^2$) ± alemtuzumab (54 mg/m$^2$). The MAC arm included patients who received Bu (12.8-16 mg/kg), cyclophosphamide (Cy) (120-200 mg/kg) ± rabbit ATG (8 mg/kg) or Bu