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Experience with Alemtuzumab, Fludarabine, and Melphalan Reduced-Intensity Conditioning Hematopoietic Cell Transplantation in Patients with Nonmalignant Diseases Reveals Good Outcomes and Risk of Mixed Chimerism Depends on Underlying Disease, Stem Cell Source, and Alemtuzumab Regimen

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A B S T R A C T

Alemtuzumab, fludarabine, and melphalan reduced-intensity conditioning (RIC) regimens are increasingly used for the hematopoietic cell transplantation (HCT) of pediatric and young adult patients with nonmalignant diseases. Early experience suggests that these regimens are associated with good survival but a high incidence of mixed chimerism, which we have previously shown to be influenced by the alemtuzumab schedule. We hypothesized that the underlying diagnosis and donor graft source would also affect the development of mixed chimerism and that the majority of patients would survive RIC HCT without graft loss. To examine this, we conducted a retrospective study of 206 patients with metabolic diseases, non-Fanconi anemia marrow failure disorders, and primary immune deficiencies who underwent 210 consecutive RIC HCT procedures at Cincinnati Children's Hospital. Ninety-seven percent of the patients engrafted. Mixed donor and recipient chimerism developed in 46% of patients. Patients with marrow failure had a low risk of mixed chimerism (hazard ratio [HR], .208; 95% confidence interval [CI], .061 to .709; $P = .012$). The risk of mixed chimerism was high in patients who received a cord blood graft (HR, 3.122; 95% CI, 1.236 to 7.888; $P = .016$). As expected, patients who received a proximal or higher dose per kilogram of alemtuzumab schedule also experienced higher rates of mixed chimerism (all HR > 2, all $P < .05$). At the time of last follow-up (median, 654 days; range, 13 to 3337), over 75% of patients had greater than 90% whole blood donor chimerism. A second transplantation was performed in 5% of patients. Three-year survival without retransplantation was 84% (95% CI, 71% to 98%) for patients who underwent transplantation with an HLA-matched sibling donor. Survival without retransplantation was negatively affected by lack of a matched related donor, increasing age, and development of grades III and IV acute graft-versus-host disease. We conclude that alemtuzumab, fludarabine, and melphalan RIC HCT offers good results for many patients and that the risk of developing mixed chimerism is influenced by underlying diagnosis, graft source, and alemtuzumab dosing.

INTRODUCTION

Reduced-intensity conditioning (RIC) hematopoietic cell transplantation (HCT) regimens have been introduced over the last 2 decades to avoid the acute toxicities and complications of myeloablative regimens. Several RIC regimens are

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reported in the literature, but in particular, RIC HCT regimens consisting of alemtuzumab, fludarabine, and melphalan are now commonly employed for pediatric and young adult patients with primary immune deficiencies and metabolic diseases, and its use is increasing for patients with marrow failure disorders. In addition to limited acute toxicities, RIC regimens that contain alemtuzumab are generally associated with a low incidence of acute graft-versus-host disease (GVHD). However, RIC regimens are often complicated by the development of mixed donor and recipient chimerism. Complete donor chimerism is not necessary to correct most nonmalignant diseases, but the development of mixed chimerism is disconcerting, because it can be associated with eventual graft loss.

To our knowledge, there are no prospective randomized studies comparing RIC to myeloablative conditioning regimens in pediatric patients with nonmalignant diseases. RIC HCT outcomes have been reported by several authors but in mostly small patient series or with heterogeneous approaches, and there are conflicting reports regarding the clinical significance of mixed chimerism [1-9]. Recent series using RIC regimens have reported high rates of primary or secondary graft failure, in 16% to 22% of patients, and the loss of cord blood grafts has been reported to occur in as many as one third to two thirds of patients [7,10,11]. In contrast, our group and the Great Ormond Street group have previously reported low rates of graft failure and retransplantation despite high rates of mixed chimerism in patients with hemophagocytic lymphohistiocytosis (HLH) and other primary immune deficiencies [2,9]. We have previously reported that the risk of mixed chimerism is influenced by the timing and dose per kilogram body weight of alemtuzumab in patients with HLH [3]. We hypothesized that the risk of mixed chimerism after alemtuzumab, fludarabine, and melphalan RIC HCT in broader patient groups would also be influenced by patient diagnosis and by the type of stem cell graft, and that like patients with HLH, the majority of patients would survive RIC HCT without graft loss. To examine this, we conducted a retrospective study of 206 patients with metabolic diseases, non-Fanconi anemia marrow failure disorders, and diverse primary immune deficiencies who underwent 210 consecutive RIC HCT procedures at Cincinnati Children's Hospital. We observed that alemtuzumab, fludarabine, and melphalan RIC HCT offers good results for many patients and that the risk of developing mixed chimerism is influenced by underlying diagnosis, graft source, and alemtuzumab dosing.

METHODS

Patients

Institutional review board permission was granted for this study. Data were abstracted from the divisional database and we also retrospectively reviewed the charts of 206 pediatric and young adult patients who underwent 210 allogeneic hematopoietic cell transplantations using alemtuzumab, fludarabine, and melphalan at our center for treatment of an underlying nonmalignant disorder between August 8, 2004 and May 22, 2013. Patient demographics are summarized in Table 1. Median patient age at the time of HCT was 4.1 years (range, .24 to 27.2 years). Patients were classified into 6 groups based on underlying diagnosis: HLH and X-linked lymphoproliferative disease (n = 91), combined immune deficiency and common variable immunodeficiency (n = 23), severe combined immune deficiency (SCID) (n = 24), non-Fanconi anemia marrow failure disorders (n = 25), metabolic disorders (n = 22), or other disorders (n = 25). The other disorders category included IPEX (n = 5), congenital enteropathy (n = 4), autoimmune lymphoproliferative syndrome (n = 3), chronic granulomatous disease (n = 2), CD25 deficiency (n = 1), DOCK8 deficiency (n = 1), hypereosinophilic syndrome (n = 1), interferon gamma receptor 2 deficiency (n = 1), Wiskott-Aldrich syndrome (n = 1), X-linked immunodeficiency with magnesium defect, Epstein-Barr virus infection, and neoplasia (n = 1), ill-defined immune deficiency (n = 2), sickle cell disease (n = 1), osteopetrosis (n = 1), and epidermolysis bullosa (n = 1). Seventy-four of the patients with HLH and X-linked lymphoproliferative disease have been reported previously [2,3].

Table 1
Patient and Transplantation Information

Characteristic	Value
No. of patients	206
No. of transplantations	210
Age at HCT, yr	
Minimum	.24
Median	4.1
Maximum	27.2
Diagnosis	
HLH, XLP	91 (43%)
CID, CVID	23 (11%)
SCID	24 (11%)
Marrow failure disorder	25 (12%)
Metabolic disorder	22 (10%)
Other	25 (12%)
HLA match	
Matched related donor	38 (18%)
Matched unrelated donor	115 (55%)
1 allele mismatch	50 (24%)
2 allele mismatch	7 (3%)
Graft source	
Bone marrow	189 (90%)
Cord blood	10 (5%)
Bone marrow + cord blood	1 (0%)
PBSC	10 (5%)
Graft TNC dose, $\times 10^8$/kg	
Minimum	.25
Median	6.80
Maximum	23.38
Graft CD34 dose, $\times 10^6$/kg	
Minimum	.06
Median	5.3
Maximum	63.0
Alemtuzumab category	
Intermediate	63 (30%)
Distal, 2.5 mg/kg or greater	40 (19%)
Distal, less than 2.5 mg/kg	35 (17%)
Proximal, greater than 1 mg/kg	23 (11%)
Proximal, 1 mg/kg or less	35 (17%)
Other	14 (7%)
GVHD prophylaxis	
Methylprednisolone, cyclosporine	147 (70%)
Methylprednisolone with tacrolimus or sirolimus	11 (5%)
Methylprednisolone, cyclosporine, methotrexate	42 (20%)
Other	10 (5%)

XLP indicates X-linked lymphoproliferative disease; CID, combined immune deficiency; CVID, common variable immune deficiency; PBSC, peripheral blood stem cells; TNC, total nucleated cell.
Data presented are n (%) unless otherwise indicated.

Transplantation Procedures

Transplantation details are summarized in Table 1. Transplantation procedures were based on published protocols [3,5,9]. Patients received fludarabine 150 mg/m^2 (5 mg/kg in patients 10 kg or less) divided over days −8 to −4 or −7 or −3 and melphalan 140 mg/m^2 (4.7 mg/kg in patients 10 kg or less) on day −3 or day −2. The dose of fludarabine was decreased by 20% for 2 patients with renal insufficiency. Because of concern for melphalan toxicity, the dose of melphalan was decreased by 25% to 50% for 2 patients with renal insufficiency, by 50% for 9 patients with a known underlying diagnosis characterized by DNA repair defects, or by 50% for 1 patient ages 2 months. The schedule of alemtuzumab was modified over the course of this report. Patients received alemtuzumab beginning on day −23, −22, or −21 (distal), −14 (intermediate), or −12, −11, −9, or −8 (proximal). Alemtuzumab was given either as a dose-escalation schedule of 3 mg, 10 mg, 15 mg, 20 mg (3 mg, 10 mg, 10 mg, 10 mg in patients less than 10 kg) or as a total of 1 mg/kg divided over 5 days, with the first dose being no more than 3 mg. Alemtuzumab was given subcutaneously in 79% of patients, as we began routine subcutaneous administration in 2007 to limit side effects of intravenous administration. For the purpose of analyses, patients were classified