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Severe Cytokine Release Syndrome after Haploidentical Peripheral Blood Stem Cell Transplantation

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Inflammatory cytokines released by activated lymphocytes and innate cells in the context of cellular therapy can cause fever, vasodilatation, and end-organ damage, collectively known as cytokine release syndrome (CRS). CRS can occur after allogeneic blood or marrow transplantation, but is especially prevalent after HLA-haploidentical (haplo) peripheral blood transplantation (PBT). We reviewed charts of all patients who underwent haplo-PBT between October 1, 2013, and September 1, 2017 and graded CRS in these patients. A total of 146 consecutive patients who underwent related haplo-PBT were analyzed. CRS occurred in 130 patients (89%), with most cases of mild severity (grade 0 to 2). Severe CRS (grade 3 to 5) occurred in 25 patients (17%). In this group with severe CRS, 13 patients had encephalopathy, 12 required hemodialysis, and 11 were intubated. Death from the immediate complications of CRS occurred in 6 patients (24% of the severe CRS group and 4% of the entire haplo-PBT cohort). The cumulative probability of nonrelapse mortality (NRM) was 38% at 6 months for the patients with severe CRS and 8% (121 of 146) in patients without severe CRS. In conclusion, CRS occurs in nearly 90% of haplo-PBTs. Older haplo-PBT recipients (odds ratio [OR], 2.4; 95% confidence interval [CI], .83 to 6.75; $P = .11$) and those with a history of radiation therapy (OR, 3.85; 95% CI, 1.32 to 11.24; $P = .01$) are at increased risk of developing severe CRS. Although most recipients of haplo-PBT develop CRS, <20% experience severe complications. The development of severe CRS is associated with a significantly increased risk of NRM.

INTRODUCTION

Blood or marrow transplantation (BMT) using related haploidentical (haplo) donors has expanded the proportion of patients eligible for this curative therapy. Historically limited by high rates of graft rejection and graft-versus-host disease (GVHD) [1,2], haplo-BMT became feasible with the advent of improved GVHD prophylaxis, such as high-dose post-transplantation cyclophosphamide (PTCy) [3,4]. Proliferating alloreactive T cells are especially sensitive to PTCy early after BMT, whereas quiescent T cells, and especially memory T cells, are relatively resistant because of their expression of aldehyde dehydrogenase [5-7]. Many large registry studies now confirm that haplo-BMT with PTCy yields results approaching those seen with matched donors, perhaps with less GVHD compared with conventional GVHD prophylaxis strategies [8-13].

Fever in the first few days of haplo-BMT has been recognized as a common occurrence [14-16]. This fever has been attributed to the release of proinflammatory cytokines by macrophages [17]. We previously reported that approximately 45% of recipients develop fever without any other signs of cytokine release syndrome (CRS) in the first 1 to 3 days after nonmyeloablative haplo-BMT, but severe CRS is rare [16]. Others have found a similarly low incidence of severe CRS after haplo-BMT, but a much higher incidence after haplo-peripheral blood stem cell transplantation (PBT) [18], with significant associated morbidity and mortality [18,19]. The higher incidence of CRS associated with PBT likely results from the presence of approximately 8-fold more T lymphocytes in peripheral blood allografts compared with bone marrow allografts [20]. No risk factors for the development of CRS after haplo-BMT other than the use of peripheral blood and conditioning regimen intensity [18,19] have been reported. Here we report our experience with CRS after haplo-PBT using PTCy, including the assessment of potential risk factors.

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METHODS

We performed a retrospective chart review of 146 consecutive patients who underwent haplo-PBT for hematologic malignancies at Johns Hopkins between October 1, 2013, and September 30, 2017. The World Health Organization's classification of hematologic malignancies was applied [21]. Patients who had undergone a previous allogeneic transplantation were excluded from consideration. In general, our practice has been to limit the use of peripheral blood grafts from haploidentical donors for first allogeneic BMT to the following situations: when marrow harvest from the donor is not practical (eg, body habitus), in the presence of diseases that appear to carry a somewhat higher risk of graft failure (eg, myelodysplastic and myeloproliferative disorders), or in patients with residual leukemia at the time of BMT. All but 1 patient received nonmyeloablative conditioning with fludarabine, cyclophosphamide, and total body irradiation 200 cGy [4]; 1 patient received myeloablative conditioning with busulfan and cyclophosphamide. All patients received GVHD prophylaxis with PTCy at 50 mg/kg on days +3 and +4, followed by mycophenolate mofetil and either tacrolimus or sirolimus starting on day +5. In May 2017, the Johns Hopkins standard of care changed from tacrolimus to sirolimus for peripheral blood allografts, in an effort to attenuate the higher rates of renal dysfunction associated with CRS.

CRS

CRS was graded according to published criteria [22]. All manifestations of CRS began in the first 5 days post-transplantation. Acute renal failure was defined as serum creatinine >2 mg/dL. All patients had a baseline creatinine of ≤1.6 mg/dL.

HLA Analysis

HLA antigen and allele mismatch in both the graft-versus-host and host-versus-graft directions was determined using a software algorithm developed in Python (by R.J.F.). Eplet mismatching was quantified using HLA-Matchmaker ABC Eplet Matching version 2.0 and DRDQDP Matching version 2.1 (http://www.hlamatchmaker.net) [23,24]. A Python script to determine the directionality of eplet mismatching (available at https://github.com/cliu32/hla-mm) [25] was modified (by R.J.F.) to incorporate the results of high-resolution typing of the *HLA-DPB1* gene.

Statistics

Patient characteristics in groups defined by CRS severity were compared using Fisher's exact test for categorical variables and the *t* test for continuous measures. Overall survival (OS) was calculated as the time from transplantation to death or last known follow-up. Progression-free survival (PFS) was calculated as the time from transplantation to death or relapse, with those receiving a second transplantation for graft failure censored at that time. All other patients without an event were censored at the last known follow-up. Administration of post-transplantation maintenance therapy to prevent relapse was not considered a progression event. OS and PFS were estimated using the Kaplan-Meier method.

Differences in time-to-event outcomes between patient groups were estimated using Cox proportional hazards models. The cumulative incidence of nonrelapse mortality (NRM) was calculated as the time from transplantation to death not due to relapse (event), death due to relapse (competing event), or last known follow-up if still alive (censored). Comparisons of time to NRM between patient groups were summarized with cumulative incidence estimates and proportional subdistribution hazards calculated using the method of Fine and Gray [26]. The cumulative incidences of both platelet and neutrophil engraftment were estimated using the same approach.

RESULTS

Patient Characteristics

The characteristics of the 146 consecutive adults who underwent haplo-PBT for a hematologic malignancy between October 1, 2013, and September 30, 2017, are summarized in Table 1. The median patient age was 63.4 years (range, 27 to 78 years), and 36.3% were female. The distributions of Disease Risk Index (DRI) and Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI) scores in our cohort were similar to those seen in our previous experience with haplo-BMT [27].

CRS

Fever between day 0 and day +5 occurred in 130 of 146 patients (89%). Fever followed a typical pattern, generally subsiding within 24 hours of the second dose of cyclophosphamide and absent in all patients by day +6. Blood cultures were positive in 7 patients (4.8%; coagulase-negative staphylococci in 6 cases and *Gordonia* species in 1 case). Mild CRS (grade 0 to 2) occurred in 121 patients. The patients with CRS had slightly shorter OS compared with the 11% of patients with no CRS, but the difference was not statistically different (hazard ratio [HR] for OS, 1.1; 95% confidence interval [CI], .5 to 2.6; $P = .83$).

Severe CRS (grade 3 to 5) occurred in 25 patients (17%). All 25 patients with severe CRS had fever, but the maximum temperature (T_{max}) did not correspond to the severity of CRS; the median

Table 1
Patient Characteristics

Characteristic	Whole Cohort (N = 146)	No or Mild CRS (N = 121)	Severe CRS (N = 25)	*P* Value
Age, yr, mean (SD)	60.4 (11.25)	59.8 (11.47)	63.2 (9.9)	.14
Conditioning intensity, n (%)				>.99
Myeloablative	1 (1)	1 (1)	0 (0)	
Nonmyeloablative	145 (99)	120 (99)	25 (100)	
Disease group, n				
MDS	34	29	5	
AML	12	12	0	
AML with MDS-related changes	23	19	4	
Therapy-related myeloid neoplasm	17	12	5	
Myeloproliferative neoplasm	15	10	5	
Chronic myelogenous leukemia	14	14	0	
Chronic lymphocytic leukemia	13	12	1	
Multiple myeloma	10	9	1	
Aggressive lymphoma	5	3	2	
Acute lymphoblastic leukemia	2	1	1	
Biphenotypic leukemia	1	0	1	
DRI, n				.11
Low	19	17	2	
Intermediate	96	75	21	
High/very high	31	29	2	
HCT-CI, n				.67
0	57	49	8	
1-2	48	38	10	
≥3	41	34	7	

MDS indicates myelodysplastic syndrome; AML, acute myelogenous leukemia.

T_{max} was 39.7 in both the mild CRS and severe CRS groups. Of the 25 patients with severe CRS, 19 (76%) developed acute kidney injury, with 12 (48%) requiring renal replacement therapy. Supplemental oxygen was required by 16 patients (64%). Moderate to severe encephalopathy occurred in 13 patients (52%), and 11 patients (42%) were intubated, most because of encephalopathy. Of the 12 patients requiring renal replacement therapy, 6 died, and 5 eventually became independent of dialysis; 1 patient was alive and dependent on intermittent hemodialysis more than 2.5 years after transplantation.

Transplantation Outcomes

For the entire cohort, the median duration of follow-up, as determined by the reverse Kaplan-Meier method, was 816 days. The median time to neutrophil recovery was 18 days (range, 12 to 98 days), and the median time to platelet recovery was 28 days (range, 11 to 202 days). Recovery of neutrophils (17 days versus 22 days; HR, .48; 95% CI, .32 to .71; $P <$ .001) and platelets (25 days versus 42 days; HR, .38; 95% CI, .23 to .61; $P <$ .001) were delayed in the patients with severe CRS compared with those with mild CRS (Figure 1A and B).

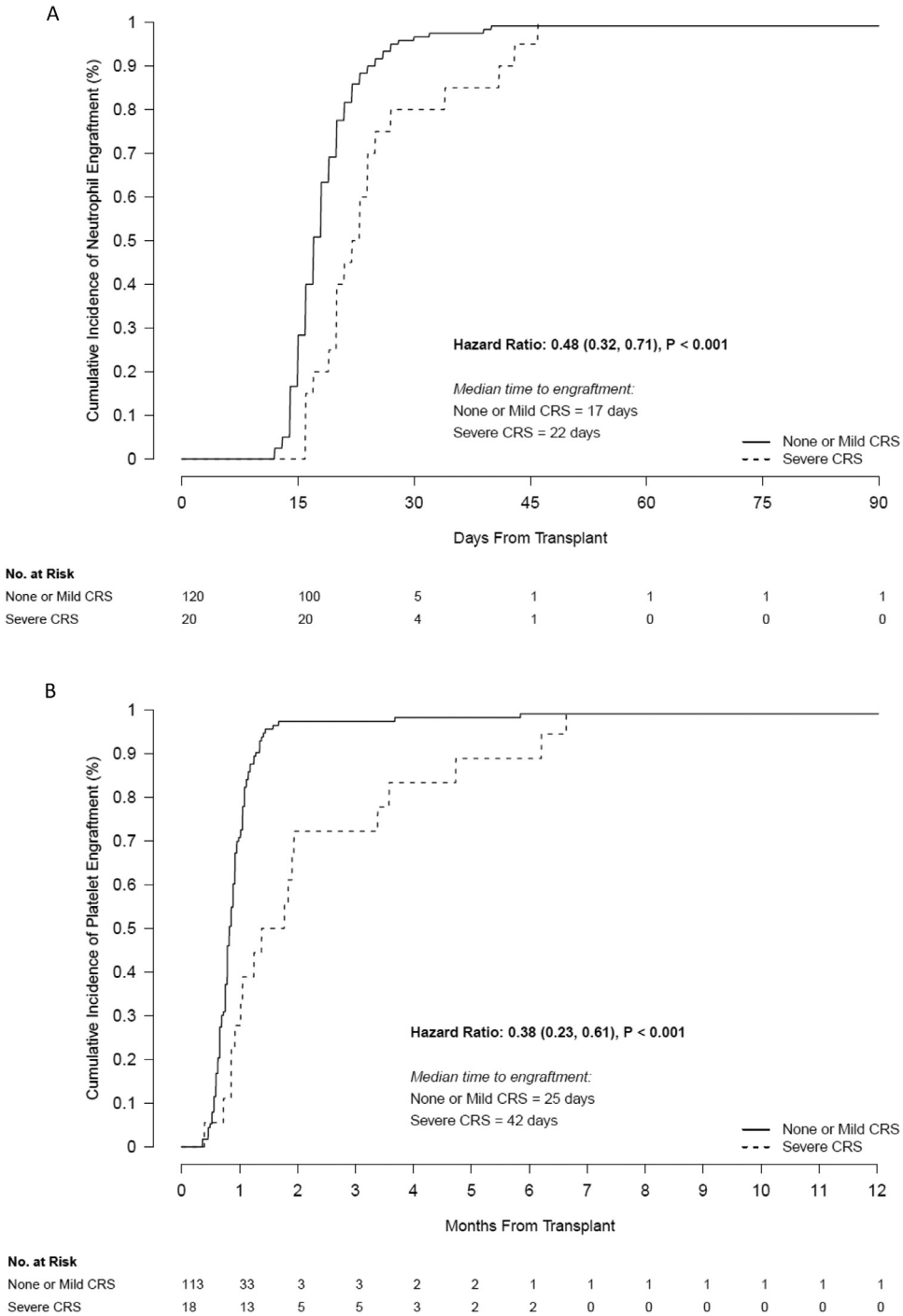
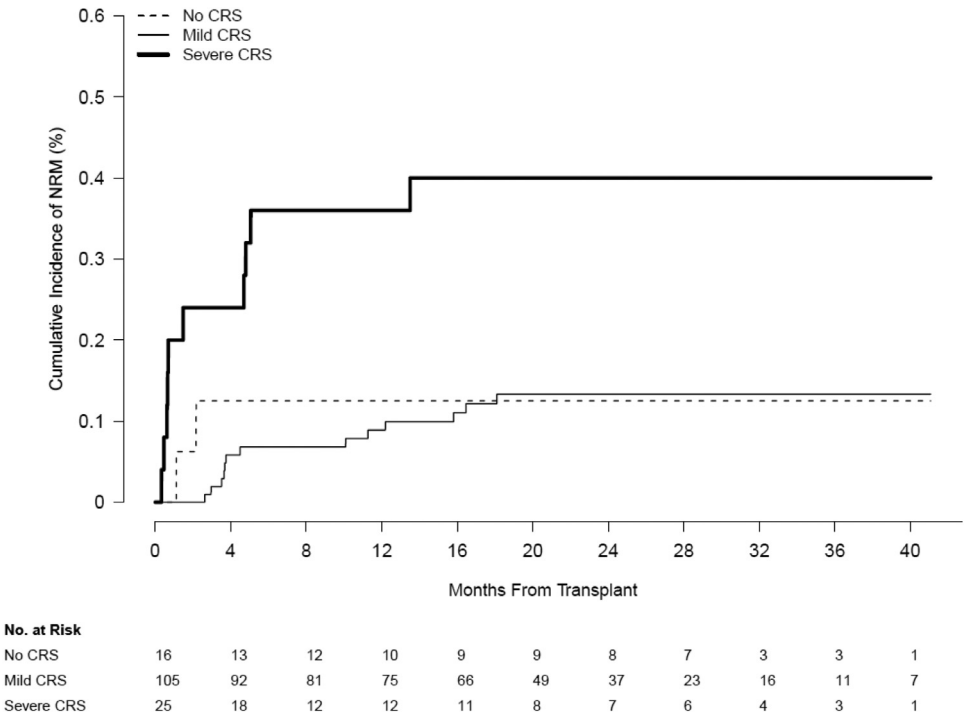


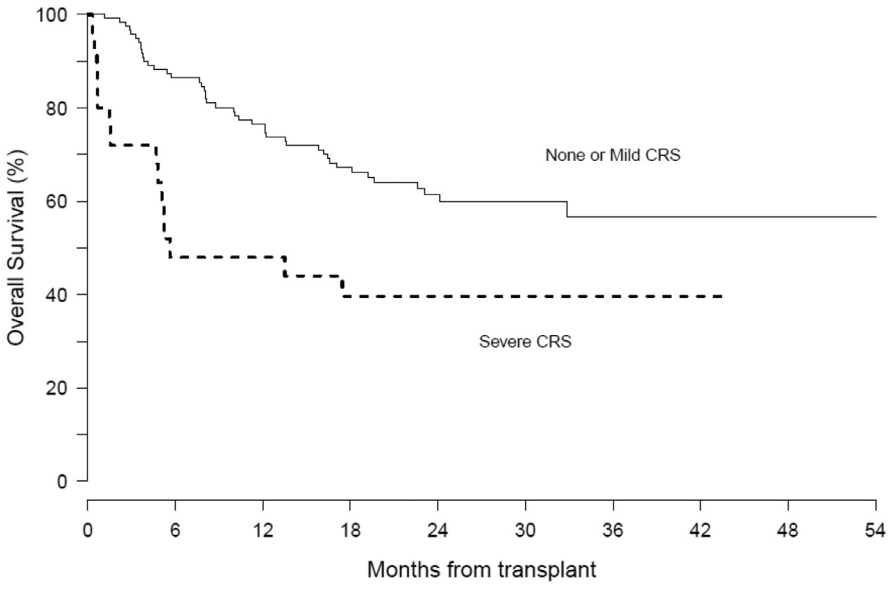
Figure 1. Neutrophil (A) and platelet (to 20,000/μL untransfused) (B) recovery by severity of CRS.



No. at Risk											
No CRS	16	13	12	10	9	9	8	7	3	3	1
Mild CRS	105	92	81	75	66	49	37	23	16	11	7
Severe CRS	25	18	12	12	11	8	7	6	4	3	1

Figure 2. Cumulative incidence of NRM according to the severity of CRS.

NRM for the entire cohort was 13% (95% CI, 7% to 18%) at 6 months and 18% (95% CI, 11% to 24%) at 2 years. There was no significant difference in NRM between patients experiencing either no CRS or mild CRS, with a cumulative incidence of 12% (95% CI, 0 to 29%) versus 7% (95% CI, 2% to 12%) at 6 months (HR, .95; 95% CI, .21 to 4.38; $P = .95$). The cumulative incidence of NRM was 38% (95% CI, 19% to 58%) in patients who developed severe CRS at 6 months, compared with 8% (95% CI, 3% to 12%) in those with mild CRS (HR, 3.97; 95% CI, 1.77 to 8.90; $P < .001$) (Figure 2). The median time to death was 171 days (95% CI, 146 to 1809 days) in the patients with severe CRS and was not reached in the group without severe CRS (HR, 2.25; 95% CI, 1.25 to 4.05; $P = .01$). In the entire cohort, OS at 2 years was 58% (95% CI, 50% to 67%) and 2-year PFS was 45% (95% CI, 38% to 55%); 2-year OS was 40% (95% CI, 24% to 65%) in the patients with severe CRS and 61% (95% CI, 53% to 72%) in those with no or mild CRS (Figure 3). In the patients with severe CRS, 6 of the 11 deaths occurred after engraftment; causes of death in the patients with severe CRS are listed in Table 2.



No. at risk										
None or Mild CRS	121	97	85	67	45	23	14	6	4	1
Severe CRS	25	12	12	9	7	5	3	1	0	0

Figure 3. Kaplan-Meier curves of OS of haplo-PBT recipients by severity of CRS.

Table 2
Causes of Death in Patients with Severe CRS

Day of Death	Cause of Death
10	Multiorgan failure
14	Pulmonary aspergillosis and respiratory failure
19	Mixed cardiogenic and septic shock (*Escherichia coli*)
20	Multiorgan failure
21	Multiorgan failure
45	Multiorgan failure
109	Respiratory failure
143	GVHD
146	Multiorgan failure
154	Respiratory failure
411	Respiratory failure

The 1-year cumulative incidence of acute grade II-IV GVHD was not different between patients with severe CRS and those with no or mild CRS (20% [95% CI, 4% to 36%] versus 27% [95% CI, 19% to 35%]; HR, .69 [95% CI, .26 to 1.81]; P= .45). There were no cases of moderate to severe chronic GVHD in patients with severe CRS, compared with 11 cases in patients with mild or no CRS (cumulative incidence at 2 years, 10%; 95% CI, 5% to 16%; P< .001 compared with severe CRS).

Rick Factors for Severe CRS

Potential risk factors for the development of severe CRS are summarized in Table 3. On univariate analysis, the development of grade 3 to 5 CRS (compared with no or mild CRS) was associated with age >60 years (OR, 2.4; 95% CI, .83 to 6.75; P = .11) and the previous receipt of high-dose radiotherapy (OR, 3.85; 95% CI, 1.32 to 11.24; P = .01). Previous radiotherapy retained the same significance after adjustment for age. The development of severe CRS was not significantly associated with the DRI or HCT-CI, although this association could not be well studied, with 21 out of 25 patients with severe CRS in the DRI intermediate-risk category and too few patients in the other categories (versus low risk: intermediate risk, OR, 2.38 [95% CI, .51 to 11.14; P = .27]; high or very high risk, OR, .59 [95% CI, .08 to 4.55; P = .61]) and too few patients with an HCT-CI score of 0 (versus 0: HCT-CI of 1 to 2, OR, 1.61 [95% CI, .58 to 4.48; P = .36]; HCT-CI ≥3, OR, 1.30 [95% CI, .43 to 3.93; P =.64]). The T_{max} at days 0 to +5 was also not different between those with severe CRS and others, with a mean T_{max} of 39.7 in both groups.

Allograft Factors

The development of CRS was not associated with either CD34 or CD3 cell dose (Table 3). Because HLA class II mismatch at DRB1 and DPB1 has been linked to fever after haplo-BMT [16], we hypothesized that class II mismatch in the graft-versus-host direction may be related to the severity of CRS. The incidence of CRS was associated with DRB1 mismatch but not with DPB1 mismatch (Table 4). There were no cases of severe CRS in patients with no DRB1 mismatches at the allele level in the GVH direction; however, there were 4 cases of severe CRS in patients with no DRB1 mismatches at the antigen level.

Table 3
Results of Univariate Analysis for Development of Severe CRS

Variable	OR (95% CI)	P Value
Age >60 yr (versus <60)	2.37 (.83-6.75)	.11
Receipt of previous radiotherapy (versus none)	3.85 (1.32-11.24)	.01
Diagnosis of TR-MN	2.27 (.72-7.15)	.16
Receipt of sirolimus (versus tacrolimus)	.73 (.23-2.31)	.59
CD3/kg recipient IBW above median (versus below)	1.34 (.56-3.19)	.51
CD34/kg recipient IBW above median (versus below)	.91 (.38-2.15)	.83

TR-MN indicates treatment-related myeloid neoplasm; IBW indicates ideal body weight.

Table 4
Association of Class II HLA Mismatch at the Allele Level in the Graft-versus-Host Direction and CRS

HLA Allele	CRS Grade 0 to 2 (N = 121), %	CRS Grade 3 to 5 (N = 25), %	P Value
DRB1			
0	14	0	
1	85	100	
2	1	0	.09
DPB1			
0	37	40	
1	62	60	
2	1	0	.86

A similar analysis using HLA class II eplets, which have been shown to predict the development of donor-specific antibodies in solid organ transplantation [28,29], showed no difference in the severity of CRS (mean ± SD mismatches, 24.0 ± 12.4 in severe CRS versus 22.5 ± 14.3 in mild CRS; P= .60) but was predictive of the development of any grade CRS (24.4 ± 13.3 mismatches versus 9.5 ± 12.6 mismatches in patients without CRS; P < .001).

Role of Immunosuppression in AKI

After changing our standard of care to include sirolimus rather than tacrolimus, the incidence of acute renal failure decreased from 16% to 8% (P = .26). The incidence of renal failure requiring dialysis did not change (8.3% with tacrolimus, 8.1% with sirolimus).

DISCUSSION

CRS occurs in 90% of haplo-PBT recipients but is severe and thus of significance in only a minority of these patients. In our cohort, severe CRS occurred in 17% of haplo-PBT recipients, and 50% of these patients died within 6 months of transplantation. Although overall outcomes in this patient population with high-risk disease are favorable, CRS is an obstacle to long-term survival.

Identification of patients susceptible to CRS, based on either host or graft characteristics, would allow targeted interventions. Among peripheral blood haploidentical grafts, we found no characteristics, including cell dose and degree of mismatch, which were reliably associated with the severity of CRS. This finding is paradoxical, given that the development of CRS is limited almost exclusively to haploidentical transplantation, and severe CRS is limited to PBT. We confirmed that class II mismatch is required for the development of CRS. The absence of HLA-DRB1 mismatch was associated with the absence of severe CRS in our cohort; this association should be confirmed in other cohorts.

The use of sirolimus in place of tacrolimus may attenuate acute kidney injury in the setting of CRS, but it does not lessen severe renal failure necessitating hemodialysis, with 8% of patients with both mild and severe CRS requiring renal replacement therapy. Renal failure associated with mild CRS is

usually reversible, and patients who survive CRS are typically able to discontinue hemodialysis.

We were able to identify host factors associated with the development of severe CRS, including older age and previous receipt of therapeutic radiation. Only 5 patients age <60 years developed severe CRS, 3 of whom had previously received radiation therapy and none of whom experienced NRM. The increased susceptibility of patients who received radiation therapy brings to mind radiation recall, which is poorly understood but involves a local memory response in a previous radiation field [30,31]. Anecdotally, several patients in our series developed toxicity in organs adjacent to the previous radiation field. The increased risk associated with previous radiation therapy is unexpected and must be considered hypothesis-generating, requiring confirmation. Some studies of CRS associated with chimeric antigen receptor T cell therapy has demonstrated that higher temperatures are associated with the development of severe CRS [32], although this was not the case in our series.

Although the difference was not statistically significant, a greater proportion of patients with severe CRS were age ≥60 years (80%) compared with those with none or mild CRS (63%). The increased susceptibility of older patients to CRS may be due to various factors. Severe CRS mimics culture-negative sepsis, and older patients have a higher incidence of and mortality from sepsis [33]. Immune dysregulation during transplantation is more pronounced in older patients [34], and increased severity of CRS may be one manifestation of this.

Decreasing circulating cytokines is an attractive therapeutic approach to prevent organ damage from CRS. We found that administration of cyclophosphamide quickly eliminated fever, with decreasing circulating cytokines the likely mechanism [19]. The fact the fever and cytokines quickly normalize by day 5 with PTCy suggests that end-organ damage has already occurred by the time PTCy is given. Tocilizumab is of uncertain benefit, and perhaps it would be surprising that lowering 1 cytokine, such as IL-6, would prevent the complications of CRS. Severe CRS is uncommon in haplo-BMT recipients. Therefore, such strategies as earlier administration of immunosuppressants (eg, tacrolimus, sirolimus, mycophenolate mofetil) aimed at limiting T cell proliferation and activation could be considered in high-risk patients receiving haplo-PBT [35].

In conclusion, CRS is an important complication that leads to increased mortality in severe cases. Overall survival for all patients who received haplo-PBT is promising. Older patients and those who have received therapeutic radiation appear to be at increased risk for severe CRS, and interventions should target primarily these patients.

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