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Immune Cytopenias after Ex Vivo CD34+-Selected Allogeneic Hematopoietic Cell Transplantation

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A B S T R A C T

Immune-mediated cytopenias (ICs), such as immune thrombocytopenia and immune hemolytic anemia, are among the adverse events after allogeneic hematopoietic cell transplantation (allo-HCT). Previous reports suggest that in vivo T cell depletion may increase the incidence of IC after allo-HCT. We evaluated whether a strategy that reduces functional donor T cells via ex vivo $CD34^+$-selection associates with the development of IC in a cohort of 408 patients who underwent allo-HCT for hematologic malignancy. The cumulative incidence of IC at 6, 12, and 36 months after the 30-day landmark post-HCT was 3.4%, 4.9%, and 5.8%, respectively. Among 23 patients who developed IC, 7 died of relapse-related mortality and 4 of nonrelapse mortality. A median 2 types of treatment (range, 1 to 5) was required to resolve IC, and there was considerable heterogeneity in the therapies used. In univariable analyses, a hematologic malignancy Disease Risk Index (DRI) score of 3 was significantly associated with an increased risk of IC compared with a DRI of 1 or 2 (hazard ratio [HR], 4.12; $P = .003$), and IC (HR, 2.4; $P = .03$) was associated with increased risk of relapse. In a multivariable analysis that included DRI, IC remained significantly associated with increased risk of relapse (HR, 2.4; $P = .03$). Our findings show that IC events occur with relatively similar frequency in patients after ex vivo $CD34^+$-selected allo-HCT compared with unmodified allo-HCT, suggesting that reduced donor T cell immunity is not causative of IC. Moreover, we noted a possible link between its development and/or treatment and increased risk of relapse.

INTRODUCTION

Immune-mediated cytopenias (ICs), such as immune thrombocytopenia (ITP) and immune hemolytic anemia (IHA), are characterized by destruction of differentiated hematopoietic cells. These events occur in 2% to 20% of allogeneic hematopoietic cell transplantation (allo-HCT) recipients, and treatment of IC in this setting is often challenging [1,2]. The mainstay of IC treatment is immunosuppression that in the early post-HCT period may hinder immune reconstitution [3]. When compared with IC in the non-HCT setting, IC after allo-HCT may be more refractory to typical up-front therapies, such as corticosteroid monotherapy, and may lead to increased overall morbidity and mortality [1,4].

The mechanisms by which IC develops after allo-HCT are poorly understood, but several have been hypothesized, including activity of alloreactive donor lymphocytes that target and destroy recipient and/or donor hematopoietic tissue and activity of recipient autoantibodies that target particular donor alloantigens [1,2,5,6]. Several prior studies describe an association between the development of IC and acute graft-versus-host disease (GVHD) in the unmodified allo-HCT setting, suggesting that persistence of residual host immune elements can precipitate IC [2,7]. Use of in vivo T cell depletion (TCD) strategies to reduce the risk of GVHD, such as peritransplant antithymocyte globulin (ATG) or alemtuzumab, have been variably associated with the incidence of IC, with some earlier retrospective reports suggesting higher rates after allo-HCT,

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particularly for nonmalignant hematologic diseases [1,4,8-12]. However, in one of the largest and most recent series to date, use of ATG or alemtuzumab was not associated with the development of IHA [1].

There are limited data on the development of IC after allo-HCT using donor allografts depleted of T cells via ex vivo $CD34^+$ selection. This GVHD prophylaxis regimen results in a higher degree of TCD than ATG- or alemtuzumab-based approaches and does not require the use of post-allo-HCT pharmacologic immune suppression. We evaluated the incidence and clinical outcomes of patients who developed IC after ex vivo $CD34^+$-selected allo-HCT and determined the initial and subsequent salvage therapies used to treat the IC events. We hypothesized that these patients would have rates of IC comparable to previous studies in the unmodified and in vivo TCD settings.

METHODS

Study Design

We conducted a retrospective analysis of IC in adult patients undergoing allo-HCT for hematologic malignancies who received ex vivo $CD34^+$-selected peripheral blood stem cell mobilized allografts using the CliniMACS CD34 Reagent System (Miltenyi Biotec, Gladbach, Germany) as GVHD prophylaxis. All patients were treated at Memorial Sloan Kettering Cancer Center (MSKCC) between 2006 and 2015. Patients received pretransplant conditioning with one of the following myeloablative conditioning regimens: busulfan, melphalan, and fludarabine; clofarabine, melphalan, and thiotepa; or high-dose (1375 cGy) total body irradiation, thiotepa, and cyclophosphamide. All regimens incorporated rabbit ATG pre-HCT to mitigate the risk of graft rejection [13-17]. The study was approved by the MSKCC institutional review board.

Patient Selection

We queried our internal MSKCC database for grade ≥3 anemias and grade ≥3 thrombocytopenia by the Common Terminology Criteria for Adverse Events, version 4.0 (National Cancer Institute). We retrospectively identified whether their anemia and/or thrombocytopenia were considered immune mediated by the treating physician requiring immune suppressive therapy. IHA and ITP events were combined as IC for statistical analyses. The exclusion criteria were primary engraftment failure, death before sustained engraftment, cytopenias in the setting of severe active infection or severe GVHD, and death or relapse before 30 days post-HCT. The primary objective was to evaluate the risk of developing IC in patients alive and relapse free at this landmark to ensure that all patients had engrafted.

Study Endpoints and Statistical Analyses

Time to IC was calculated from 30 days after allo-HCT until the date of IC, relapse, death, or last contact. The cumulative incidence of IC was estimated by considering relapse and death as competing risk events. Patient and HCT characteristics were assessed for association with development of IC using Cox regression models, and the cause-specific hazard ratios (HRs) were estimated. Patient and HCT characteristics included age, gender, disease, conditioning regimen, HLA match, and ABO compatibility. Disease risk was assessed using the validated Disease Risk Index (DRI), and comorbidities were assessed using the Hematopoietic Cell Transplantation Comorbidity Index [18,19]. We explored the prognostic impact of IC on overall survival (OS), progression-free survival (PFS), relapse, and nonrelapse mortality (NRM). From the 30-day landmark time, OS and PFS were estimated by the Kaplan-Meier method [20]. Relapse and NRM were estimated using cumulative incidence functions and were considered competing events. We also estimated event-time distribution of each endpoint starting from the clinical onset date for the subset of patients who experienced IC. IC was analyzed as a time-dependent variable such that at the start of follow-up, all patients were classified as having no IC and grouped as having IC at event onset. This approach appropriately credited event-free time prior to IC onset to the no IC group [21]. Univariable analyses were performed using Cox regression models. Cause-specific HRs were estimated for the analysis of relapse and NRM. Multivariable analyses were performed for each outcome for which univariable analysis identified a significant association with IC. Variables with $P < .20$ on univariable analysis were included in the final multivariable Cox regression models. Two-sided P values $< .05$ were considered significant. Statistical analyses were performed using R version 3.2.4 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient and IC Characteristics

Patient and HCT characteristics for all evaluated patients are shown in Table 1. A total of 408 patients were alive and relapse free 30 days after allo-HCT. The median follow-up among survivors was 35 months (range, 5 to 117) after the 30-day landmark. Among 408 patients in the analysis, 23 developed IC at a median onset of 189 days after allo-HCT (range, 39 to 840), and 184 patients relapsed or died without IC. Of the 23 patients who developed IC, IHA occurred in 10 (43%), ITP occurred in 10 (43%), and both (Evans syndrome) occurred in 3 (13%) [22]. The cumulative incidence of IC at 6, 12, and 36 months after the 30-day landmark was 3.4% (95% confidence interval [CI], 1.7% to 5.2%), 4.9% (95% CI, 2.8% to 7%),

Table 1
Patient Characteristics and Association with Development of IC

Characteristic	All Patients*N (%)	Patients with ICN	HR (95% CI)	*P* Value
Median age, yr (range)	56 (21-72)	54 (25-69)	.98 (0.95-1.01)	.28
Gender				
Female	178 (43)	10	1.00 (Reference)	.91
Male	230 (57)	13	1.05 (0.46-2.39)	
Disease				
Acute leukemia & MDS	277 (68)	17	1.00 (Reference)	.44
MM	94 (23)	3	.62 (0.18-2.1)	.78
Other hematologic malignancy	37 (9)	3	1.19 (0.35-4.06)	
Conditioning				
Chemo based	309 (76)	16	1.00 (Reference)	.56
TBI based	99 (24)	7	1.3 (0.53-3.16)	
DRI				
1-2	355 (87)	16	1.00 (Reference)	.003
3	45 (11)	6	4.12 (1.61-10.6)	.37
Not evaluable	8 (2)	1	2.54 (0.34-19.2)	
ABO mismatch				
None	189 (46)	12	1.00 (Reference)	.34
Minor	104 (26)	9	1.52 (0.64-3.61)	.07
Major	115 (28)	2	0.26 (0.06-1.14)	
HLA match				
MRD	140 (34)	6	1.00 (Reference)	.38
MUD	268 (66)	17	1.52 (0.6-3.85)	NA
• MUD (10/10)	184 (45)	14	NA	NA
• MUD (1-allele mismatch)	84 (21)	3	NA	

MDS indicates myelodysplastic syndrome; MM, multiple myeloma; TBI, total body irradiation; MRD, matched related donor; MUD, matched unrelated donor; NA, not available.

* All evaluated patients at risk for IC.

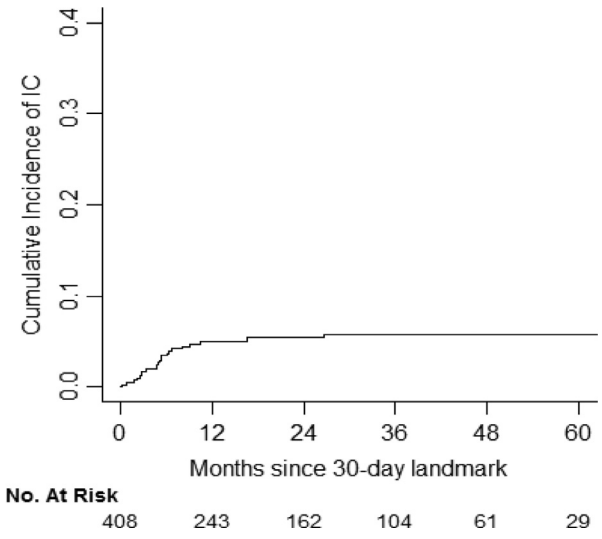

Figure 1. Cumulative incidence of IC.

and 5.8% (95% CI, 3.5% to 8.1%), respectively (Figure 1). In most IC patients (19; 83%), the condition resolved after treatment at a median of 72 days (range, 15 to 259) after event onset. Eleven patients who developed IC died (48%): 7 of relapse and 4 of NRM. Four patients (17%) died without resolution of their IC. Only 1 patient (4%) with IHA died because of IC. Two patients with ITP experienced serious bleeding complications: one a subdural hematoma and the other a mediastinal hematoma. The time to IC event, time from IC start to IC resolution, and time from IC resolution to relapse or NRM are shown in Figure 2. A median of 2 types of treatment (range, 1 to 5) were required for resolution of IC. Intravenous immunoglobulin (IVIG; 74%), corticosteroids (65%), and rituximab (48%) were the most commonly used treatments for IC. A summary of all clinical approaches used for the IC events among all patients and individual patients is shown in Table 2 and Table 3, respectively. Among all patient and HCT characteristics, a DRI score of 3 conferred a significantly increased risk of IC compared with risk scores of 1 or 2 (HR, 4.12; 95% CI, 1.61 to 10.56; $P = .003$). Patient age, gender, disease, conditioning regimen, HLA match, and ABO compatibility were not associated with an increased risk of IC (see Table 1).

Association of IC and Treatment Outcomes

The 3-year cumulative incidence of relapse from the +30-day landmark was 23.9% (95% CI, 19.6% to 28.2%). In patients who developed IC, the 6-month cumulative incidence of relapse after IC onset was 30% (95% CI, 13% to 50%). Among all patient and HCT characteristics in a univariable analysis, development of IC (HR, 2.4; 95% CI, 1.1 to 5.2; $P = .03$), having multiple myeloma (HR, 2.4; 95% CI, 1.6 to 3.7; $P < .001$), and a DRI score of 3 (HR, 3.3; 95% CI, 2.0 to 5.3; $P < .001$) were associated with an increased risk of relapse. In a multivariable analysis, development of IC (HR, 2.4; 95% CI, 1.1 to 5.2; $P = .03$), having multiple myeloma (HR, 2.9; 95% CI, 1.9 to 4.6; $P < .001$), and a DRI score of 3 (HR, 3.9; 95% CI, 2.4 of 6.5; $P < .001$) were associated with an increased risk of relapse. The 6-month PFS after IC onset was 57% (95% CI, 40% to 81%). Among all patient and HCT characteristics in a univariable analysis, development of IC (HR, 1.9; 95% CI, 1.02 to 3.5; $P = .04$), having multiple myeloma (HR, 1.9; 95% CI, 1.4 to 2.5; $P < .001$), and a DRI score of 3 (HR, 2.3; 95% CI, 1.6 to 3.3; $P < .001$) were associated with an inferior PFS. In a multivariable analysis, development of IC was not significantly associated with PFS after controlling for multiple myeloma (HR, 2.1; 95% CI, 1.5 to 2.9; $P < .001$) and a DRI score of 3 (HR, 2.4; 95% CI, 1.7 to 3.6; $P < .001$).

The 3-year cumulative incidence of NRM from 30 days post-HCT was 24.5% (95% CI, 20.1% to 28.8%). In the patients who developed IC, the 6-month cumulative incidence of NRM after IC onset was 13% (95% CI, 3.1% to 30.3%). Among all

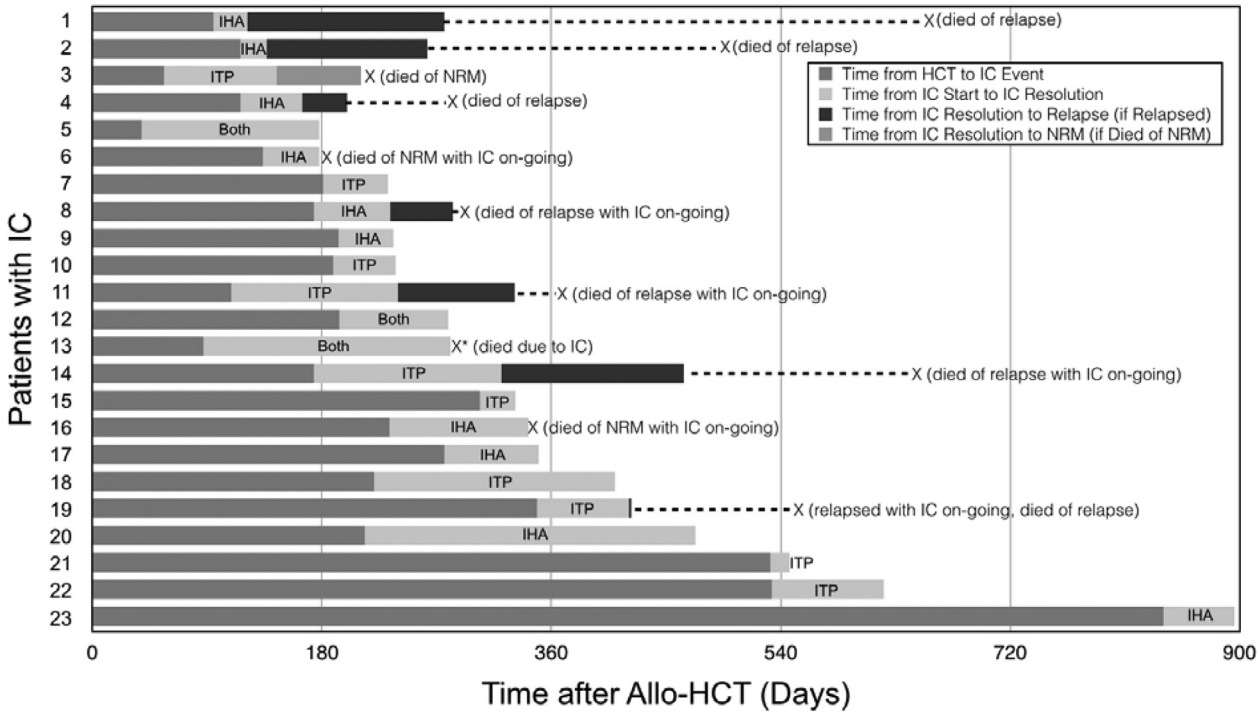

Figure 2. Summary of outcome events in patients with IC. All patients were alive at their last follow-up unless otherwise indicated. (X, died; X*, died due to IC.)

Table 2
Summary of All Clinical Treatments for IC (N = 23)

Clinical Treatments	N (%)
Immunologic event	
IHA	10 (43)
ITP	10 (43)
Both (Evans syndrome)	3 (13)
Initial treatment used	
Corticosteroids	6 (26)
IVIG	13 (57)
Corticosteroids + IVIG	1 (4)
Rituximab	2 (9)
CNI + IVIG	1 (4)
All treatments used	
Corticosteroids	15 (65)
IVIG	17 (74)
Rituximab	11 (48)
CNI	5 (22)
Romiplostim	2 (9)
Splenectomy	5 (22)
Other	6 (26)

CNI indicates calcineurin inhibitor.

patient and HCT characteristics in a univariable analysis, age (per year) (HR, 1.02; 95% CI, 1.0 to 1.04; $P = .03$) and minor ABO mismatch (HR, 1.8; 95% CI, 1.1 to 2.8; $P = .017$) were associated with an increased risk of NRM. Patients who received total body irradiation-based conditioning had a reduced risk of NRM (HR, 0.53; 95% CI, 0.31 to 0.92; $P = .024$). No multivariable analysis was performed, because IC was not found to be a risk factor for NRM.

The median OS from 30 days post-HCT for all patients was 73.3 months (95% CI, 47 to not reached). In patients with IC, 6-month OS after IC onset was 74% (95% CI, 58% to 94%). Among all patient and HCT characteristics in a univariable analysis, development of IC (HR, 1.9; 95% CI, 1.01 to 3.5; $P = .05$), older age (per year) (HR, 1.02; 95% CI, 1.01 to 1.03; $P = .005$), having multiple myeloma (HR, 1.7; 95% CI, 1.2 to 2.4; $P = .002$), minor ABO mismatch (HR, 1.4; 95% CI, 1.01 to 2.1; $P = .04$), and a DRI score of 3 (HR, 2.3; 95% CI, 1.5 to 3.4; $P < .001$) were associated with an increased risk of death from any cause. In a multivariable analysis, IC was not significantly associated with OS, but older age (per year) (HR, 1.04; 95% CI, 1.0 to 1.05; $P < .001$), having multiple myeloma (HR, 2.3; 95% CI, 1.6 to 3.4; $P < .001$), and a DRI score of 3 (HR, 2.3; 95% CI, 1.5 to 3.4; $P < .001$) were associated with an increased risk of death from any cause. Table 3 presents the clinical treatments used in each IC patient.

Table 3
Clinical Treatments Used in Each IC Patient

Patient	Treatments Used
1	Rituximab
2	Corticosteroids, CNI
3	IVIG
4	Corticosteroids
5	IVIG, rituximab, CNI, splenectomy
6	IVIG
7	Corticosteroids, IVIG, rituximab, splenectomy
8	Corticosteroids, rituximab
9	Corticosteroids
10	IVIG
11	IVIG, corticosteroids, rituximab, romiplostim, splenectomy
12	IVIG, other
13	Corticosteroids, IVIG, other, splenectomy
14	IVIG, corticosteroids, rituximab
15	Corticosteroids, rituximab
16	IVIG, corticosteroids, rituximab, other
17	IVIG, CNI, rituximab, corticosteroids, other, splenectomy
18	IVIG, corticosteroids, romiplostim, rituximab, CNI, other
19	IVIG, corticosteroids
20	Rituximab, IVIG, corticosteroids, CNI, other
21	IVIG
22	IVIG, corticosteroids
23	IVIG

DISCUSSION

Previous studies have reported highly variable rates of IC after allo-HCT depending on the HCT platform, disease type, and use of in vivo TCD [9,12,23]. In a large cohort of patients undergoing ex vivo CD34$^+$-selected allo-HCT, we found that IC events occur with relatively low and similar frequency compared with more recent reports of IC in the unmodified allo-HCT [1]. Furthermore, although all patients in our series received ATG as part of their conditioning regimen, which could potentially further negatively affect normal immune reconstitution in the post-HCT period, this conditioning did not appear to affect the incidence of IC, which is a relatively rare allo-HCT complication in our patients [24,25]. It is possible that the true overall incidence of IC in patients undergoing ex vivo CD34$^+$-selected allo-HCT may be under-reported in our analysis, particularly because cases of anemia or thrombocytopenia reported as lower than grade 3 were not included. However, it is likely that most previously published retrospective reports of IC after allo-HCT similarly excluded indolent or unrecognized events.

Notably, we found that the treatments used for patients with IC were highly variable, and resolution of IC often required use of multiple immunosuppressive agents in most patients. Congruent with reported outcomes in unmodified allo-HCT, the response to corticosteroids, and monotherapies in general, were suboptimal in our cohort, suggesting that adjunctive therapies should be added very early in the treatment of IC after ex vivo CD34$^+$-selected allo-HCT. However, the optimal adjunctive therapy and/or combination therapies remains uncertain, particularly given that the precise etiology of IC events has not been fully elucidated [26].

In multivariable analysis, we found that having an IC event was associated with an increased risk of disease relapse. It should be noted that patients with IC also had proportionally higher DRI scores than those without IC. Importantly, however, the multivariable model for relapse suggested that IC was independently associated with higher relapse rates when accounting for other significant factors, including DRI. Although our analysis was not designed to elucidate these findings, it is feasible that patients who develop IC are at an increased risk of relapse and poorer overall outcomes; they receive additional immune suppressive therapy that may further hinder appropriate immune reconstitution after allo-HCT. This additional treatment is particularly relevant in the context of ex vivo CD34$^+$-selection after which T cell immune recovery is prolonged [3,25,27].

Moreover, adult patients undergoing ex vivo CD34$^+$-selected allo-HCT appear to be at a similar risk of developing IC as patients receiving unmodified allografts, on the basis of historical reports [1,2]. The appropriate therapy to treat IC after ex vivo CD34$^+$-selected allo-HCT is poorly defined, but our experience suggests that early combination therapy may be more effective than corticosteroid monotherapy. To fully understand how IC and its treatment affect immune recovery, it will be of interest to examine specific immune effector populations before and after the IC event. Although the relatively low incidence of IC in these patients makes it difficult to formulate a definitive conclusion, the relationship between IC and the DRI is compelling and should be investigated in larger studies.

Table 4
Multivariable Analyses of Outcomes in Patients with IC

Characteristic	Relapse HR (95% CI)	PFS HR (95% CI)	OS HR (95% CI)
IC	2.4 (1.1-5.2)*	1.8 (0.9-3.4)^{NS}	1.7 (0.9-3.4)^{NS}
Age, per yr	NA	1.02 (1-1.03)*	1.04 (1.02-1.05)**
Gender			
Male versus female	1.3 (0.82-1.9)^{NS}	1.1 (0.8-1.5)^{NS}	NA
Disease			
MM versus acute leukemia	2.9 (1.9-4.6)**	2.1 (1.5-2.9)**	2.3 (1.6-3.4)**
Other versus acute leukemia	1.3 (0.6-2.7)^{NS}	0.9 (0.5-1.6)^{NS}	0.5 (0.3-1.07)^{NS}
Conditioning			
TBI versus chemotherapy	NA	NA	1.7 (1.03-2.8)*
DRI			
3 versus 1-2	3.9 (2.4-6.5)**	2.4 (1.7-3.6)**	2.3 (1.5-3.4)**
ABO mismatch			
Minor versus none	NA	1.1 (0.8-1.6)^{NS}	1.3 (0.9-1.8)^{NS}
Major versus none	NA	1.0 (0.7-1.4)^{NS}	1.0 (0.7-1.5)^{NS}
HLA match			
MUD versus MRD	0.6 (0.4-0.95)*	NA	NA

Values are HR (95% CI). Variables with $P < .20$ on univariable analysis were included in the final multivariable Cox regression models.
NS indicates not significant.
* $P < .05$;
** $P < .001$.

Table 4 presents multivariable analyses of outcomes in patients with IC.

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