Efficacy of immune suppression tapering in treating relapse after reduced intensity allogeneic stem cell transplantation

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ABSTRACT

For patients who relapse after allogeneic hematopoietic stem cell transplantation while still on immune suppression, there is anecdotal evidence that tapering the immune suppression may result in graft-*versus*-tumor activity. We reviewed the medical records of all patients with documented histological or radiographic disease recurrence within 1 year of stem cell transplantation while on immune suppression at our institution. The median time to relapse was 110 days (range, 18-311) after transplant. Among 123 patients with relapse treated with immune suppression tapering without chemotherapy, radiation, or donor lymphocyte infusion, 34 responded (33/101 reduced intensity conditioning transplant and 1/22 myeloablative conditioning transplant, 32.7% and 4.5% respectively; *P*=0.007). The median time to response after initiation of immune suppression tapering was 82 days (range, 16-189). Thirty-three patients (97.1%) had development or progression of acute or chronic graft-*versus*-host disease as a consequence of immune suppression tapering, at a median time of 39 days (range, 16-98). Six patients subsequently relapsed late after initial response to immune suppression tapering at a median time of 2 years (range, 0.9-3.8). The median overall survival from immune suppression tapering for responders was 5.1 years (range, 1.9-not estimable). When clinically feasible, immune suppression tapering alone in patients who relapse early after reduced intensity conditioning allogeneic stem cell transplantation can produce durable remissions, but is almost always associated with graft-*versus*-host disease.

Introduction

The graft-*versus*-tumor effect, mediated primarily by donor-derived T cells, is the driving force underlying the efficacy of allogeneic hematopoietic cell transplantation (HCT). Direct evidence of the graft-*versus*-tumor effect was established with the observation that donor lymphocyte infusions (DLI) as a solitary treatment could induce complete and often durable remissions in patients who had relapsed after HCT.[1-4]

In 2010, the National Cancer Institute published their first conference report on the treatment of relapse after allogeneic HCT.[5] This report acknowledged that there is currently no standard approach to the treatment of relapse after HCT, but that many transplant physicians start with the withdrawal of immune suppression, with or without DLI, further chemotherapy, or second HCT. The withdrawal of immune suppression is thought to lead to activation of donor T cells against the tumor cells. Although a commonly used strategy, the efficacy of immune suppression withdrawal as a treatment for relapse has not been formally documented. Several case reports and case series have demonstrated response to immune suppression tapering in lymphoma[6-9] and myelodysplastic syndromes/acute myeloid leukemia.[10] One analysis examined 307 patients who had recurrent or persistent acute leukemia, chronic myeloid leukemia in blast phase, or advanced myelodysplastic syndrome after HCT and had received at least one relapse-directed intervention. Almost 90% of patients had undergone myeloablative conditioning (MAC) in this study and relapse interventions included withdrawal of immune suppression, chemotherapy, and/or DLI. Withdrawal of immune suppression alone was no different at inducing remission than chemotherapy alone [hazard ratio (HR)=0.92, (95% confidence interval) (95% CI 0.5-1.9)] or chemotherapy in addition to immune suppression withdrawal (HR=1.35, 95% CI 0.7-2.6).[11]

In our patients who relapse after reduced intensity conditioning (RIC) HCT, we have observed a number of individuals with both myeloid and lymphoid malignancies who experienced durable responses to immune suppression tapering alone without any additional chemotherapy, radiation, or DLI. Herein we describe the clinical characteristics of these patients, the time course and durability of their responses, and the complications subsequently encountered.

Methods

Clinical factors were extracted from the Dana Farber transplantation database and medical chart review. This study was approved by the Dana-Farber/Harvard Cancer Center institutional review board.

Documented relapse was defined as recurrence or progression of disease after HCT. Relapse or progression of myelodysplastic syndrome was defined as new or worsening cytopenias after HCT and progression on bone marrow biopsy. Relapse or progression of myelodysplastic syndrome was defined as new or increased blast count in the peripheral blood or bone marrow. Relapse or progression of lymphoma was defined as new or increased disease on imaging; biopsy was not required. Another cohort of patients undergoing immune suppression tapering because of falling peripheral blood total

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leukocyte donor cell chimerism with development of cytopenias was identified (deemed at risk of relapse after HCT).

RIC was defined as a cumulative intravenous busulfan dose of 3.2-6.4 mg/kg, or melphalan 100-140 mg/m^2 with fludarabine 120-125 mg/m^2. MAC consisted of cyclophosphamide with fractionated total body irradiation (1200-1400 cGy in 7 fractions), or high-dose busulfan with cyclophosphamide. The disease risk index was calculated as previously described.[12] Patients undergoing "immune suppression tapering alone" had reduction or withdrawal of immunosuppression without cytotoxic chemotherapy including hydroxyurea or radiation. Immunosuppression was defined as the administration of calcineurin inhibitors, sirolimus, mycophenolate mofetil, or steroids. Complete response was defined as complete recovery of peripheral blood counts, absence of disease in marrow, negative radiological imaging, or total donor cell chimerism recovery to above 90%. Partial response was defined as improvement in disease burden, but without a complete response. This included any decrease in peripheral blood blasts, decrease in size of lymph nodes or chloromas, or improvement in cytopenias and chimerism but not to normal levels.

Statistical analysis

Descriptive statistics were used to summarize patients' baseline characteristics. The Fisher exact test or chi-square test was used to compare categorical variables and the Wilcoxon rank sum test was used to compare continuous variables. Overall survival for the cohort in which immune suppression was tapered was defined as the time from the start of immune suppression tapering to death from any cause. Overall survival for patients with documented relapse was defined from the date of documented relapse to death from any cause. Relapse-free survival for the cohort managed with immune suppression tapering was defined from start of tapering to relapse or death, whichever occurred first. Overall and relapse-free survival rates were estimated using the method of Kaplan-Meier, with 95% confidence intervals calculated using the Greenwood formula. Kaplan-Meier curves were compared using the log-rank test. Prognostic factors for response to immune suppression tapering and overall survival were examined in Cox proportional hazards models. Cumulative incidences for non-relapse death and relapse with or without death were estimated reflecting time to relapse and time to non-relapse death respectively as competing risks. For the cohort undergoing immune suppression tapering, multivariable logistic regression analysis was performed to identify factors that are associated with response to the tapering. A backward selection approach was used to select the final model in multivariable analysis. All *P* values are two-sided with a significance level of 0.05. All statistical analyses were performed using SAS 9.3 (SAS Institute Inc, Cary, NC, USA), and R version 2.13.2 (the CRAN project).

Table 1. Baseline characteristics of patients responding to immune suppression tapering alone.

Characteristic (n, %)	Documented relapse (n=34)	Falling chimerism (n=14)
Age (median years and range)	58 (27-70)	62.5 (49-73)
Gender		
Male	24 (70.6)	13 (92.9)
Female	10 (29.4)	1 (7.1)
Disease		
Acute myeloid leukemia	8 (23.5)	3 (21.4)
Myelodysplastic syndrome	9 (26.5)	4 (28.6)
Lymphoma	11 (32.3)	1 (7.1)
Chronic lymphocytic leukemia	4 (11.8)	2 (14.3)
Myeloproliferative neoplasm	0	4 (28.6)
Multiple myeloma	2 (5.9)	0
Disease risk index		
Low	4 (11.8)	4 (28.6)
Intermediate	16 (47.1)	6 (42.9)
High	12 (35.3)	4 (28.6)
Very high	2 (5.9)	0
Prior autologous HCT	8 (23.5)	1 (7.1)
Disease status at time of HCT		
Complete remission	7 (20.6)	5 (35.7)
Partial remission	12 (35.3)	2 (14.3)
Induction failure	10 (29.4)	2 (14.3)
Untreated	5 (14.7)	5 (35.7)
Donor		
Matched related	12 (35.3)	3 (21.4)
Matched unrelated	19 (55.9)	8 (57.1)
Mismatched unrelated	3 (8.8)	3 (21.4)
Patient/donor cytomegalovirus		
Positive/positive	7 (20.6)	2 (14.3)
Positive/negative	11 (32.4)	3 (21.4)
Negative/positive	7 (20.6)	4 (28.6)
Negative/negative	9 (26.5)	5 (35.7)
Graft source		
Peripheral blood stem cells	34 (100)	13 (92.9)
Bone marrow	0	1 (7.1)
Conditioning regimen for HCT		
Myeloablative	1 (2.9)	0
Reduced intensity	33 (97.1)	14 (100)
GVHD prophylaxis for HCT		
Tacrolimus/methotrexate	8 (23.5)	3 (21.4)
Tacrolimus/sirolimus	7 (20.6)	1 (7.1)
Tacrolimus/sirolimus/methotrexate	17 (50)	10 (71.4)
Tacrolimus/methotrexate/bortezemib	2 (5.9)	0
HCT to relapse (median days and range)	109.5 (18-311)	98.5 (53-360)

Results

Between January 1, 2004 and December 31, 2012, 2009 allogeneic HCT were performed at Dana Farber Cancer Institute/Brigham and Women's Hospital, of which 810 employed MAC and 1199 employed RIC. Documented relapses occurred in a total of 535 patients (26.6%) within 1 year of HCT, of whom 463 were receiving immune suppression at the time of relapse (124 with MAC and 339 with RIC). Out of 463 post-HCT relapses, 340 underwent chemotherapy or radiation while 123 underwent immune suppression tapering alone for relapse treatment. Patients who underwent chemotherapy or radiation were younger, more likely to be female, less likely to have myeloid disease, and more likely to have undergone MAC HCT (*Online Supplementary Table*).

For patients on immune suppression at the time of relapse, 123 out of 463 (26.7%) underwent immune suppression tapering as the only therapy for relapse (22 MAC and 101 RIC). Thirty-four of these 123 patients (27.6%) responded to immune suppression tapering alone without need for additional therapy: 33/101 RIC and 1/22 MAC (32.7% and 4.5%, respectively; *P*=0.007). Table 1 presents the baseline characteristics of the 34 patients with documented relapse who responded to immune suppression tapering alone. Their median age was 58 years (range, 27-

70). Half of patients (50.0%) underwent HCT for acute myeloid leukemia or myelodysplastic syndrome. Fourteen patients (41.2%) had a high or very high disease risk index at the time of HCT. The transplant was from a matched, related donor in 12 patients (35.3%), a matched, unrelated donor in 19 patients (55.9%) and a mismatched, unrelated donor in three patients (8.8%). All patients received a tacrolimus-based regimen for GVHD prophylaxis. At the time of starting immune suppression tapering, 21 patients (61.8%) were on tacrolimus and sirolimus, eight patients (23.5%) were on only tacrolimus, two patients (5.9%) were on only sirolimus, one patient (2.9%) was on tacrolimus and prednisone, one patient (2.9%) was on prednisone and mycophenolate mofetil and one patient (2.9%) was on tacrolimus, prednisone and mycophenolate mofetil. Three patients had active GVHD at the time of relapse.

Of the 34 patients who responded to immune suppression tapering alone, 23 attained a complete response (Table 2). The median time to response was 82 days (range, 16-189). The median time between starting to taper immune suppression and coming off immune suppression completely was 28 days (range, 0-837). Six patients (17.6%) could not come off immune suppression completely because of the development of GVHD during tapering of the immune suppression. Thirty-three patients (97.1%) had development or progression of acute and/or chronic GVHD at a median time of 39 days (range, 16-98) after starting to taper the immune suppression. Out of 22 patients who developed acute GVHD, eight (36.4%) had grade III-IV GVHD. The median times to onset of acute GVHD and chronic GVHD after tapering immune suppression were 31 days (range, 16-98) and 57 days (range, 21-486), respectively. In contrast, among the patients who did not respond to immune suppression tapering alone, 40% developed

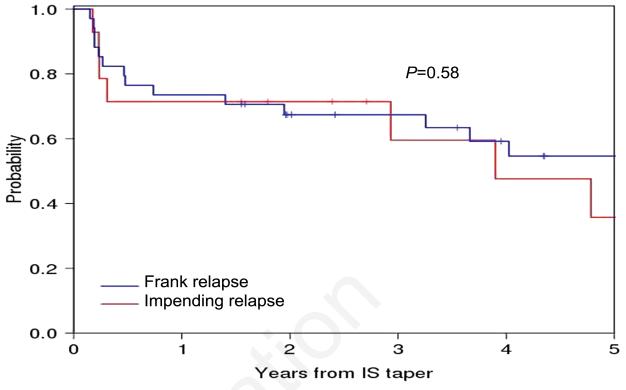

Figure 1. Overall survival of patients responding to immune suppression tapering (IS taper) alone. Overall survival from the initiation of IS taper. The median overall survival of patients with frank relapse and those with impending relapse (patients with falling chimerism) was not different, being 5.1 years (range 1.9-not estimable) and 3.9 years (range 0.24-not estimable), respectively.

Table 2. Results of patients responding to immune suppression (IS) tapering alone.

	Documented relapse (n=34)	Falling chimerism (n=14)	*P*
Age at relapse (years)	58 (27-70)	62 (49-73)	0.09
Time from starting to completing IS tapering*	28 days (0-837)	106 days (9-243)	0.06
Response to IS tapering			
Complete response	23 (67.6%)	12 (85.7%)	
Partial response	11 (32.4 %)	2 (14.3 %)	
Time to documented response	82 days (16-189)	48 days (14-182)	0.29
GVHD from IS tapering			
Acute grade I-IV	22 (64.7%)	8 (57.1%)	0.75
Time to developing acute GVHD after IS tapering	31 days (16-98)	38 days (14-183)	0.66
Chronic	24 (70.6%)	9 (64.3%)	0.74
Time to developing chronic GVHD after IS tapering	57 days (21-486)	126 days (14-1186)	0.72
Any GVHD**	33 (97.1%)	13 (92.9%)	0.5
Time to developing any GVHD after IS tapering	39 days (16-98)	53 days (14-261)	0.49
Relapse after IS tapering			
Second relapse after IS tapering	6 (17.6%)	3 (21.4%)	1
Median time to second relapse	2 years (0.9-3.8)	3.9 years (2.4-3.9)	0.053
Median relapse-free survival	3.7 years (1.1-NE)	3.9 years (0.24-NE)	
4-year relapse-free survival	46%	38%	0.87
Overall survival from time of IS tapering			
Median overall survival	5.1 years (1.9-NE)	3.9 years (0.24-NE)	
4-year overall survival	59%	48%	0.58
Cause of death	Disease (n=4), GVHD (n=5), Infection (n=5), CHF (n=1), IPS (n=1), Unknown (n=1)	Disease (n=2), GVHD (n=4), Infection (n=2)	0.69

**: 12 patients could not come off IS completely due to GVHD; **: either I-IV acute or chronic GVHD whichever occurs first; NE: not estimable; CHF: chronic heart failure; IPS: idiopathic pneumonia syndrome.*

GVHD in the absence of DLI or a second HCT. Five of the 34 responders to immune suppression tapering (14.7%) died from GVHD or its complications. Six patients (17.6%) relapsed again after an initial response to immune suppression tapering at a median of 2 years after the first relapse (range, 0.9-3.8). The median overall survival and relapse-free survival of the 34 patients who responded to immune suppression tapering was 5.1 years (range, 1.9-not estimable) and 3.7 years (range, 1.1-not estimable), respectively. The median follow-up time among survivors was 4.2 years (range, 1.6-9.3). The 1- and 2-year cumulative incidence of non-relapse mortality after immune suppression tapering was 26.5% and 32.4%, respectively (Table 2).

Of 123 patients undergoing immune suppression tapering without chemotherapy or radiation, 89 did not have an initial response to this tapering. Of these non-responders, 21 went on to receive DLI and eight went on to receive a second HCT. The median time to DLI or second HCT was 58 days (range, 15-466). The time to DLI or second HCT was not different for patients with myeloid or lymphoid diseases, being 56 days (range, 29-466) and 59.5 days (range, 15-119), respectively (P=0.72). Of note, 24/29 (82.8%) underwent DLI or second HCT before the median time of documented response to immune suppression tapering (82 days).

In univariable analysis of patients with documented relapse who underwent immune suppression tapering alone (n=123), diagnosis and conditioning regimen intensity were the only factors associated with response to this tapering. Seventeen of 95 patients (17.9%) with myeloid disease and 17/28 (60.1%) with lymphoid disease responded to immune suppression tapering alone (P<0.0001). As regards conditioning regimen, 33/101 patients (23.7%) given RIC and 1/22 (4.5%) given MAC responded to immune suppression tapering alone (P=0.007). Of note, the median bone marrow blast percentage of patients with acute myeloid leukemia or myelodysplastic syndrome who responded (n=14) or not (n=50) to immune suppression tapering alone was 9% (range, 1-47%) and 12% (range, 2-92%), respectively (P=0.12). There were an additional 21 non-responders who did not have a bone marrow biopsy performed at relapse because of circulating disease. In these patients, the median blast percentage in the peripheral blood was 21% (range, 3-79%). Looking at blasts in the bone marrow or peripheral blood, there was a trend towards a higher blast count in the non-responders to immune suppression tapering than in the responders (15% *versus* 9%; P=0.056). Patients' age and gender, donor gender, donor type, graft source, GVHD prophylaxis, cytomegalovirus status and disease risk index were not significantly different between responders and non-responders to immune suppression tapering, although there was a trend towards higher disease risk index in the non-responders (P=0.054) (Table 3). In the multivariable model, myeloid disease (OR=0.14, 95% CI 0.054-0.37; P<0.0001) and MAC (OR=0.1, 95% CI 0.012-0.83; P=0.033) were associated with a lower likelihood of responding to immune suppression tapering alone. Factors included in the multivariable models were patients' age at relapse, donor and recipient gender, donor type (HLA-matched related or unrelated, HLA-mismatched related or unrelated and umbilical cord blood donors), graft source (peripheral blood stem cells or bone marrow), cytomegalovirus status of donor and recipient, conditioning intensity (MAC or RIC), disease (myeloid *versus* lymphoid), high disease risk index, and GVHD prophylaxis. Examining the impact of chimerism in patients given RIC, responders had a higher level of total donor cell chimerism compared to non-responders (median 93 *versus* 80%, respectively; P=0.009) and a higher proportion of patients with chimerism of 90% or higher at the time of tapering immune suppression (63.3% *versus* 32.3%; P=0.007).

In univariable analysis for overall survival, response to immune suppression tapering as a time-dependent variable was significantly associated with better overall survival (HR=0.52, 95% CI 0.28-0.97; P=0.039). In a multivariable model for overall survival, a diagnosis of myeloid *versus* lymphoid disease (HR=5.12, 95% CI 2.71-9.66; P<0.0001), MAC *versus* RIC (HR=2.22, 95% CI 1.35-3.68) and HLA-mismatched unrelated *versus* HLA-matched related donor

Table 3. Patients with documented relapse who underwent immune suppression tapering without chemotherapy or radiation, divided by response to the tapering.

Characteristic (n. %)	Non-responders (n=89)	Responders (n=34)	P
Age at HCT, median (range)	58 (21-71)	58 (27-70)	0.28
Patients' gender			
Male	59 (66.3)	24 (70.6)	0.83
Female	30 (33.7)	10 (29.4)	
Diagnosis			
Acute myeloid leukemia	61 (68.5)	9 (26.5)	<0.0001
CLL/SLL/PLL	1 (1.1)	4 (11.8)	
Hodgkin disease	3 (3.4)	4 (11.8)	
MM/PCD	1 (1.1)	2 (5.9	
Acute lymphocytic leukemia	2 (2.2)	0	
MDS	10 (11.2)	8 (23.5)	
MPD	6 (6.7)	0	
Mixed MDS/MPD	1 (1.1)	0	
Non-Hodgkin disease	4 (4.5)	7 (20.6)	
Myeloid diagnosis	78 (87.6)	17 (50.0)	<0.0001
HLA type (at A, B, DRB1)			
Matched unrelated	48 (35.9)	19 (55.9)	0.6
Matched related	25 (28.1)	12 (35.3)	
Mismatched unrelated	15 (16.9)	3 (8.8)	
Mismatched related	1 (1.1)	0	
Conditioning intensity			
Myeloablative	21 (23.6)	1 (2.9)	0.007
Reduced intensity	68 (76.4)	33 (97.1)	
Graft source			
Bone marrow	6 (6.7)	0	0.14
PBSC	76 (85.4)	34 (100)	
Bone marrow & PBSC	2 (2.2)	0	
Umbilical cord blood	5 (5.6)	0	
GVHD prophylaxis			
Tacrolimus/sirolimus/methotrexate	40 (44.9)	16 (47.1)	0.75
Tacrolimus/methotrexate	21 (23.6)	7 (20.6)	
Tacrolimus/sirolimus	18 (20.2)	8 (23.5)	
Tacrolimus/other	6 (6.7)	3 (8.8)	
MMF/other	4 (4.5)	0	
Disease risk index			
Low	1 (1.1)	4 (11.8)	0.054
Intermediate	40 (44.9)	16 (47.1)	
High	40 (44.9)	12 (35.3)	
Very high	8 (9.0)	2 (5.9)	

CLL: chronic lymphocytic leukemia; SLL: small lymphocyte lymphoma; PLL: prolymphocytic leukemia; MM/PCD: multiple myeloma/plasma cell disorder; MDS: myelodysplastic syndrome; MPD: myeloproliferative disease; PBSC: peripheral blood stem cells; MMF: mycophenolate mofetil.

(HR=2.35, 95% CI 1.26-4.39) were the only factors associated with inferior overall survival in patients treated with immune suppression tapering alone.

Patients with falling chimerism

Among 37 patients who developed cytopenias with a fall in total donor-derived hematopoietic cell chimerism but without formal evidence of disease recurrence, 14 (37.8%) responded to immune suppression tapering alone; all had received RIC. The patients' characteristics are outlined in Table 1. There was no difference in response rates, GVHD from immune suppression tapering or relapse-free survival between the cohorts with documented relapse and falling chimerism (Table 2). There was also no difference in overall survival between patients with documented relapse and falling chimerism (4-year overall survival: 59% *versus* 48%, respectively; *P*=0.58) (Figure 1).

Discussion

Rapid withdrawal of immune suppression is a common initial approach in the management of disease relapse after HCT. The decision to pursue or add further therapy such as chemotherapy, radiation, DLI or second HCT is generally at the discretion of the physician, without clear guidelines regarding how immune suppression tapering fits into these options. Several small case series have reported clinical responses to immune suppression tapering alone, although details regarding interval to response, durability, and complications have been sparse. One series of patients with lymphoma who relapsed after allogeneic HCT showed a 42% response rate to reduction in immune suppression as initial therapy for relapse.[9] The largest series of patients with acute myeloid leukemia and myelodysplastic syndrome undergoing RIC HCT showed that only three out of 48 patients managed with immune suppression tapering for relapse responded to this therapy alone, although most patients went on to other therapies very quickly after relapse, making it difficult to assess the response to the decreasing immune suppression alone.[10] In this current large single institution series spanning a decade, we demonstrate that immune suppression tapering alone can induce a significant and long-lasting graft-*versus*-tumor effect, although almost always in concert with the development or progression of GVHD. The 4-year overall survival of all patients treated with immune suppression tapering alone was 24%, but among responders, the 4-year overall survival was 59%. We identified a second cohort of patients who underwent rapid immune suppression tapering for falling total donor cell chimerism who also responded to this management.

It is important to note that the median time to response to immune suppression tapering was 82 days in this study, which indicates that this strategy may only be relevant for patients with more indolent diseases or relapses. Indeed, in this study patients with more indolent diseases, such as myelodysplastic syndromes and non-Hodgkin lymphoma, were more likely to respond to immune suppression tapering than those with more aggressive diseases, such as acute myeloid leukemia (Table 3). There was also a trend towards a higher disease risk index and higher blast count in patients who did not respond to immune suppression tapering alone than in those who did respond.

Patients responding to immune suppression tapering as the only mode of treatment for relapse had almost exclusively undergone RIC HCT. It is possible that patients relapsing early after HCT have not had time to develop a full graft-*versus*-tumor effect, which can be promoted by accelerated immune suppression tapering. Patients who relapse after MAC HCT have already demonstrated resistance to high-dose chemotherapy/radiation which may also signal some degree of insensitivity to immune manipulation. Furthermore, patients undergoing RIC are more likely to have mixed chimerism early after HCT, and conversion to full chimerism with immune suppression tapering could coincide with a graft-*versus*-tumor effect.

The majority of patients responding to immune suppression tapering did develop GVHD. This suggests that the development of GVHD is associated with response. All patients who developed GVHD after immune suppression tapering were treated with steroids with or without restarting low-dose sirolimus or tacrolimus. In all patients surviving with GVHD, therapy significantly improved the symptoms of GVHD. Of 12 patients who were treated with tacrolimus or sirolimus in addition to steroids, only three relapsed, and all at more than 1 year after the first relapse. This indicates that reinstating immune suppression in patients who develop GVHD does not abrogate graft-*versus*-tumor effects. Patients needing treatment for GVHD after tapering immune suppression were generally still on low-dose immune suppression at 1 year after the initial attempt to withdraw the immune suppression.

A limitation of our analysis is that patients were not prospectively selected to undergo immune suppression tapering. The timing of the tapering, the pace at which medications were withdrawn and the subsequent use of DLI or second HCT were at the discretion of the physician. The favorable results of the patients who responded to immune suppression tapering alone compared to the results of those needing chemotherapy or radiation were also likely skewed as the former are more likely to be subjects who had lower disease burden or more indolent relapses, and could avert the need for cytoreductive chemotherapy or radiation while waiting for a response to the immune suppression tapering.

In conclusion, immune suppression tapering alone could lead to sustained remissions and long-term survival in patients with disease relapse early after RIC HCT. These responses are almost always associated with the development of acute and/or chronic GVHD. Because a response often takes many weeks to become evident, clinicians should exercise patience after immune suppression tapering, when clinically feasible, to allow sufficient time for the graft-*versus*-tumor effect. If there is no evidence of rapidly progressive disease, this strategy potentially avoids the toxicity associated with more aggressive therapies such as chemotherapy or DLI. Understanding the clinical, molecular and immunological characteristics of underlying disease will allow us to predict better who will respond to this manipulation.

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Authorship and Disclosures

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