HHS Public Access

Author manuscript

Bone Marrow Transplant. Author manuscript; available in PMC 2012 December 01.

Published in final edited form as:

Bone Marrow Transplant. 2012 June ; 47(6): 804–809. doi:10.1038/bmt.2011.180.

Allogeneic Hematopoietic Cell Transplantation in Patients with Myelodysplastic Syndrome and Concurrent Lymphoid Malignancy

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Abstract

Allogeneic hematopoietic cell transplantation (HCT) can be curative for both myelodysplastic syndromes (MDS) and lymphoid malignancies. Little is known about the efficacy of allogeneic HCT in patients in whom both myeloid and lymphoid disorders are present at the time of HCT. We analyzed outcomes in 21 patients with MDS and concurrent lymphoid malignancy when undergoing allogeneic HCT. Seventeen patients had received extensive prior cytotoxic chemotherapy, including autologous HCT in seven, for non-Hodgkin lymphoma (NHL, n=7), Hodgkin lymphoma (HL, n=2), chronic lymphocytic leukemia (CLL, n=5), NHL plus HL (n=1), multiple myeloma (n=1), or T-cell acute lymphocytic leukemia (ALL) (n=1), and had, presumably, developed MDS as a consequence of therapy. Four previously untreated patients had CLL. Nineteen patients were conditioned with high-dose (n=14) or reduced-intensity regimens (n=5), and transplanted from HLA-matched or one antigen/allele mismatched related (n=10) or unrelated (n=9) donors; two patients received HLA-haploidentical related transplants following conditioning with a modified conditioning regimen. Currently, 2 of 4 previously untreated, and 2 of 17 previously treated patients are surviving in remission of both MDS and lymphoid malignancies. However, the high non-relapse mortality among previously treated patients, even with reduced-intensity conditioning regimens, indicates that new transplant strategies need to be developed.

Keywords

concurrent MDS and lymphoid malignancy; conditioning regimens; secondary MDS; relapse

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

INTRODUCTION

Myelodysplastic syndrome (MDS) is a well described complication of cytotoxic chemotherapy as treatment for lymphoid malignancies.[1–4] It may occur after non-transplant cytotoxic therapy or after autologous hematopoietic cell transplantation (HCT). In fact, published data suggest that MDS after autologous HCT is related to pre-HCT therapy.[1,5] Occasionally, however, MDS is diagnosed in previously untreated patients simultaneously with lymphoma.[6–9] Allogeneic HCT offers potentially curative treatment for both disease entities, including patients who have failed to respond to non-transplant therapy.[10,11] We and others have previously reported experience with allogeneic HCT for patients with therapy-related MDS following treatment for lymphoid malignancies, but without evidence of the primary disease at the time of HCT.[12,13] In the present study, we identified patients who underwent allogeneic HCT for MDS, but concurrently had an active lymphoid malignancy, either diagnosed simultaneously with MDS or preceding the diagnosis of MDS. Patients with antecedent lymphoid malignancies had received cytotoxic therapy. Patients included in this report were treated over an extended time interval during which treatment strategies have evolved. However, the data should draw attention to this patient population for which more effective therapeutic options must be developed.

PATIENTS AND METHODS

From a database of 1100 patients with MDS or related disorders who underwent allogeneic HCT at the Fred Hutchinson Cancer Research Center (FHCRC) from 1990 through 2009, 21 patients were identified who, in addition to MDS, had an active lymphoid malignancy present at the time of HCT. The study was approved by the Institutional Review Board of the FHCRC.

Patients without prior cytotoxic therapy

Four patients had never received cytotoxic chemotherapy, and MDS appeared to represent a *de novo* disorder (Cohort A, Table 1). These patients ranged in age from 41 to 65 (median 57) years at the time of HCT. The MDS subtypes according to WHO Classification are shown in Table 1. Median percentage of marrow myeloblasts was 9.3%. Two of the four patients had good-risk cytogenetics (normal karyotype) , and two had an intermediate-risk karyotype by International Prognostic Scoring System (IPSS) criteria.[14] The IPSS scores ranged from 0.5 to 2.0 with a median score of 0.5. All four patients were diagnosed concurrently to also have chronic lymphocytic leukemia/ small lymphocytic lymphoma (CLL/SLL), stage 0. All patients received high-dose conditioning followed by hematopoietic stem cell infusion from HLA-matched related or unrelated donors. Further details are provided in Table 1.

Patients who had received prior cytotoxic therapy

Seventeen patients, 29–71 (median 50.4) years of age, had previously received cytotoxic therapy (Cohort B, Table 1). Among these, seven had undergone high-dose chemotherapy followed by autologous HCT. Details are provided in Table 1. In addition to MDS, five patients had concurrent CLL, while the remainder had other lymphoid malignancies

including follicular lymphoma, diffuse large B cell (DLBCL) Non-Hodgkin lymphoma (NHL), HL,or multiple myeloma. One patient had T-cell ALL. Five patients had good -risk, one intermediate-risk, and 11 high-risk/ complex karyotypes. The median marrow myeloblast percentage was 11.3%. In 14 of 17 patients there was marrow involvement by the lymphoid malignancy. Supradiaphragmatic or infradiaphragmatic lymph node enlargement was present in both patients with HL, in 5 of 7 patients with NHL, and in the patient with HL and DLBCL. CLL was Rai stage 0 in one patient, stage I in 1 patient, and stage IV in the remaining 3 patients. The patient with myeloma was staged as Durie-Salmon stage I. Ten patients were conditioned with high-dose regimens, while five patients received low-intensity conditioning regimens. The remaining two patients were transplanted with marrow from haploidentical children following conditioning with a modified reduced-intensity regimen (see Table 1).

Source of stem cells

The stem cell source was bone marrow in one of four patients with primary MDS, while three patients were given G-CSF mobilized peripheral blood stem cells (PBSC). In patients with secondary MDS, nine received marrow and eight received G-CSF mobilized PBSC as a source of stem cells.

Conditioning regimens

Conditioning regimens varied and were dependent upon patient age, comorbidity, disease stage, donor availability, and the type of research protocol active at the Center at the time of the patients' HCT. Four patients were conditioned with fludarabine (Flu) at 30 mg/m^2/day i.v. for 3 consecutive days and 2 Gy of total body irradiation (TBI). Three patients received Flu ,30 mg/m^2/day for 5 days, plus cyclophosphamide (Cy) 2×14.5 mg/kg i.v., and 2 Gy TBI. Three patients received Cy, 60 mg/kg i.v., for 2 consecutive days and 6 × 2 Gy of TBI over three 3 days. Four patients received busulfan (Bu), prescribed dose 16 mg/kg p.o., over 4 days (with dose adjustments to achieve steady state plasma levels of 800–900 ng/mL [targeted Bu]) plus Cy, 60 mg/kg i.v., for two 2 consecutive days. The remaining patients received Flu, 40 mg/m^2/ day i.v., for 3 days, and targeted Bu starting with a prescribed dose of 16 mg/kg; Flu, 40 mg/m^2/day i.v., for 5 days, and targeted Bu with anti-thymocyte globulin (ATG; Atgam); or targeted Bu over 4 days plus Cy, 60 mg/kg/day i.v., for 2 days plus ATG.[15]

GVHD prophylaxis and therapy—Graft -versus -host disease (GVHD) prophylaxis consisted of cyclosporine (CSP)[16] and methotrexate (MTX)[17] in 12 patients, tacrolimus[18] and MTX in 4, CSP and mycophenolate mofetil (MMF) in 4, tacrolimus and MMF in 1, and CSP alone in 1 patient. The diagnosis of acute and chronic GVHD were made by established criteria.[19,20]

Assessment of results

Engraftment, GVHD and relapse were assessed as previously described.[15,21,22] Patients who died with evidence of persistent or recurrent disease – MDS or lymphoid malignancy – were considered to have died from MDS/lymphoid malignancy, regardless of the immediate cause of death. All other deaths were considered to be related to non-relapse causes.

Data were analyzed as of July 19, 2010.

RESULTS

Engraftment

All patients with primary MDS (Table 2) achieved neutrophil engraftment (>0.5 × 10^9 /L for three days) by day 28. Among patients with secondary MDS, 15 patients achieved neutrophil engraftment; two patients died early (at 14 and 7 days, respectively) from non-relapse causes and, thus, were not evaluable for engraftment (Table 2). All remaining patients had achieved engraftment by day 44.

GVHD—Among patients with primary MDS (Cohort A), two (50%) developed acute GVHD grades I–II, and two developed chronic GVHD. Among patients with secondary MDS (Cohort B), 13 of 15 evaluable patients (87%) developed acute GVHD, grades I–II in 10, and grades III–IV in 3 patients, and 7 of 13 patients at risk developed chronic GVHD (Table 2).

Relapse—Among four patients with primary MDS, two (50%) showed persistence of CLL and eventually relapsed with MDS. Among 17 patients with secondary MDS one (patient 7) died too early to assess for clearance of the disease. Among the remaining 16 patients, the lymphoid malignancy persisted in three (patients 9, 10 and 15), which was not unexpected as clonal cells in these disorders often clear only gradually.[23] However, two patients (patients 9 and 15) died with progression of their lymphoid malignancy and associated complications, while one patient (patient 10) died with relapsed MDS. In the remaining 13 patients, both myeloid and lymphoid malignancies cleared after HCT before relapse was documented in four of them (Table 2).

Survival—The median follow-up for all patients was 6.2 months. At the time of analysis, 2 of 4 patients with primary MDS were alive without evidence of disease at 14 and 4 years after HCT, respectively. Two patients had died with relapse of MDS and CLL at 5.1 and 46 months, respectively (Table 2).

Among patients with secondary MDS, 2 of 17 patients were alive at the time of analysis, in apparent remission of MDS and lymphoid malignancy, at 11.9 and 15 years after HCT, respectively. Nine patients died from non-relapse causes, and six from disease relapse. For all 17 patients the median relapse-free survival was 4.3 months, and the median overall survival was 6.2 months (Table 2).

DISCUSSION

We identified 21 patients who underwent allogeneic HCT for MDS in the setting of a concurrent lymphoid malignancy. In four patients the concurrent diagnoses of MDS and lymphoid malignancy were established simultaneously prior to any therapy. Seventeen patients received a diagnosis of MDS following a preceding diagnosis of and therapy for their lymphoid malignancy and, therefore, were considered to have secondary MDS. Our findings are consistent with previous studies, which have shown the presence of various

lymphoid malignancies in association with MDS.[6] Also consistent with previous reports is the fact that the most frequent lymphoid malignancy among patients with MDS was CLL.[6]

The relationship between primary MDS and lymphoid malignancies is unclear. While MDS is considered a myeloid disorder, it can, rarely, transform to acute lymphocytic leukemia.[24] Furthermore, in an experimental xenotransplantation model of MDS, identical clonal abnormalities have been demonstrated in lymphoid and myeloid precursors.[25] Consistent with such a model, MDS-associated cytogenetic abnormalities have been observed in circulating lymphoid cells in MDS patients.[26] However, in the majority of reports of lymphoid malignancies associated with MDS, there has been no evidence of a common cell of origin.[7–9,27] As both disorders occur with increasing frequency at older age, the simultaneous diagnosis of two malignancies may be a coincidence. By the age of 60 years about 3% of the population express small B cell clones, and progression to CLL has been observed.[28,29] It is conceivable that immunological abnormalities associated with MDS may facilitate such a progression.[30,31]

The development of MDS following treatment for other malignancies, including lymphoid neoplasms is well documented.[1,2,32] As observed here, those patients typically show higher risk features, in particular high -risk cytogenetics, than do patients with de novo MDS.[1] The 17 patients considered here had received cytotoxic chemotherapy, but showed persistent or recurrent evidence of their lymphoid malignancies at the time of HCT for MDS. Thus, the transplant was undertaken in an attempt to eradicate both MDS and lymphoid malignancy. Treatment failures among patients with de novo MDS were related to relapse of either MDS or CLL. Among patients with secondary MDS, relapses of either myeloid or lymphoid malignancy (or both) occurred in seven patients, but mortality was due primarily to non-relapse causes. The most prominent causes of death were related to infections. As all these patients had previously received cytotoxic therapy, often with multiple agents and for multiple cycles, increased non-relapse mortality was expected.

It was of note in the cohort with secondary MDS, that patients experienced relapse of one, but not the other disease, suggesting that a given conditioning regimen was effective in eradicating myeloid or lymphoid malignant cells, but not both. However, these data should be interpreted with great caution as the tumor burden of the two malignancies may have differed significantly. Also, the follow-up for some of these patients was short.

Of the five patients conditioned with low -intensity conditioning regimens, three died from non-relapse causes as did 6 of 10 patients conditioned with higher -intensity regimens. Both patients who underwent haploidentical transplants died from relapse. Nevertheless, two patients with de novo MDS and CLL (one transplanted from a related and one from an unrelated donor) are surviving in remission from both diseases, as are two patients with secondary MDS, whose original lymphoid malignancies were HL and NHL, respectively.

Taken together, these data suggest that patients with MDS and concurrent lymphoid malignancies, diagnosed simultaneously or metachronously, should not, *a priori* be excluded from consideration of transplantation. However, both relapse and non-relapse mortality were high, and better tolerable regimens must be developed, particularly for patients with

secondary MDS. As therapy given for the initial diagnosis of a lymphoid malignancy may vary greatly, "custom-designed" conditioning regimens should aim at minimizing toxicity that may develop on the background of previously administered therapy. Conceivably, post-HCT adjuvant therapy, for example with hypomethylating agents,[33] directed at MDS or with rituximab directed at certain lymphoid malignancies, might reduce the relapse risk without adding to transplant-related toxicity.

Acknowledgments

We thank all patients for consenting to these studies, the physicians and nurses caring for the patients, Franchesca Nguyen for maintaining the database, and Helen Crawford and Bonnie Larson for help with manuscript preparation.

The authors are grateful for research funding from the National Institutes of Health, Bethesda, MD grants P01HL036444, P01CA078902, P01CA018029, and K23HL084054. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health nor its subsidiary Institutes and Centers.

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Table 1

Demographic and transplant characteristics

Patient No.	MDS Subtype	Marrow Blast (%)	IPSS	Karyotype	Lymphoid Malignancy	Age at Tx (years)	Donor / Cell Source	Conditioning	GVHD prophylaxis
Cohort A: No prior cytotoxic therapy									
1	RA	4	0.5	46 XY	CLL	65	MRD / BM	Cy 120mg/kg / TBI 10 Gy	CSP / MTX
2	RAEB	6	0.5	46,XY	CLL	63	MRD / PBSC	Flu 3×40 mg/m^2 / tBu	CSP / MTX
3	ET/MF/MDS	1	N/A	48,XY,+8,+9	CLL	61	MRD / PBSC	Flu 5×40 mg/m^2 / tBu / ATG	FK / MTX
4	RAEB	18	2	46,XX,add(2)(q37)	CLL	41	URD / PBSC	tBu / Cy 120mg/kg	FK / MTX
Cohort B: Prior cytotoxic therapy[a]									
5	RA	<1	0	46XY	CLL	49	URD / BM	Cy 120 mg/kg / TBI 6×2 Gy	CSP / MTX
6	RAEB/AML	50	2.5	46XY	MM	52	URD / BM	Cy 120 mg/kg / TBI 6×2 Gy	CSP / MTX
7	RAEB	7	3	Complex	HL	47	MRD / BM	Cy 120 mg/kg / tBu	CSP / MTX
8	RA/AML	31	N/A	Complex	HL	41	URD / BM	Cy 120 mg/kg / TBI 6×2 Gy	CSP / MTX
9	RA	<1	0.5	46xy	CLL	52	MRD / PBSC	Cy 120 mg/kg / tBu	CSP / MTX
10	RARS	<1	0.5	Complex	CLL	64	MRD / PBSC	Flu 90 mg/m^2 / TBI 2 Gy	FK / MMF
11	RA	4	0	46,XY,del(20) (q11.2q13.3)	FL (grade III)	50	MMURD[b] / PBSC	Cy 120 mg/kg / TBI 6×2 Gy	FK / MTX
12	RA	4	0.5	47,XY,+8	HL + DLBCL	49	MRD / BM	Cy 120 mg/kg / TBI 6×2 Gy	CSP / MTX
13	CMML	21	2.5	46,XY,del(20) (q11.2q13.3)	CLL	51	URD / PBSC	Cy 120 mg/kg / tBu / ATG	CSP / MTX
14	RA	4	1.5	Complex	CLL	50	URD / BM	Cy 120 mg/kg / tBu	CSP / MTX
15	RA	<1	1	Complex	FL	55	MRD / PBSC	Flu 90 mg/m^2 / TBI 2 Gy	CSP / MMF

Patient No.	MDS Subtype	Marrow Blast (%)	IPSS	Karyotype	Lymphoid Malignancy	Age at Tx (years)	Donor / Cell Source	Conditioning	GVHD prophylaxis
16	RA	<1	1	Complex	DLBCL	29	URD / BM	Cy 120 mg/kg / tBu	CSP / MTX
17	RAEB	13	2.5	Complex	T-ALL	37	Haploidentical sibling / BM	Flu 30 mg/m^2 / Cy 14.5 / mg/kg[d] TBI 2 Gy	FK / MMF
18	RA	2	1.5	Complex	FL	51	MRD / PBSC	Flu 90 mg/m^2 / TBI 2 Gy	CSP / MMF
19	RA	5	1	Complex	FL	52	URD / PBSC	Flu 90 mg/m^2 / TBI 2 Gy	CSP / MMF
20	RA	4	1	Complex	DLBCL	57	MMURD[c] / PBSC	Flu 150 mg/m^2 / TBI 2 Gy	FK / MTX
21	RA	4	1	Complex	DLBCL	71	Haploidentical sibling / BM	Flu 150 mg/m^2 / Cy 29 mg/kg[d] / TBI 2 Gy	FK / MMF

Patients 15–21 had previously received autologous HCT.

[a] The intensity of cytotoxicity and the numbers of cycles given varied widely.

[b] A antigen, B allele mismatched.

[c] B allele mismatched.

[d] Patients also received Cy, 50 mg/kg, on day 3 after transplantation.

Abbreviations: AML= acute myeloid leukemia arising from MDS; ATG= antithymocyte globulin; BM= bone marrow; Bu=busulfan; CLL= chronic lymphocytic leukemia; CMML= chronic myelomonocytic leukemia; CSP / MTX= cyclosporine + methotrexate; Cy= cyclophosphamide; DLBCL= diffuse large B-cell lymphoma; ET/MF/MDS= Essential thrombocythemia evolving to myelofibrosis and transforming to myelodysplastic syndrome; FK= tacrolimus; FL= follicular lymphoma; Flu= fludarabine; GVHD= graft-versus-host disease; HL= Hodgkin lymphoma; IPSS= International Prognostic Scoring System; MDS= myelodysplastic syndrome; MM= multiple myeloma; MMF= mycophenolate mofetil; MMURD= HLA-mismatched URD; MRD= HLA-matched related donor; N/A= not applicable; PBSC= G-CSF mobilized peripheral blood progenitor cells; RA= refractory anemia; RAEB= refractory anemia with excess blasts; RARS= RA with ring sideroblasts; T-ALL= T-cell acute lymphoblastic leukemia; TBI= total body irradiation; tBu= busulfan starting at 1 mg/kg every 6 hours, for 16 doses, but with dose adjustment to achieve pre-determined trough levels at doses 5, 9, and 13; Tx= transplantation; URD= HLA-matched unrelated donor.

Table 2

Transplant outcome

Patient No.	Acute GVHD(grade/organs involved)	Chronic GVHD	Relapse	Outcome / COD	Prior Autologous Transplant	RFS (ms)	OS (ms)
Cohort A							
1	Grade I (skin)	Yes	No	Alive	No	>170.3	>170.3
2	grade II (skin + gut)	N/A	Relapse MDS / Persistent CLL	Relapse	No	4.5	5.17
3	No	No	Relapse MDS / Persistent CLL	Relapse	No	26.8	46
4	No	Yes	No	Alive	No	>46.5	>46.5
Cohort B							
5	II (skin + gut)	N/A	No	Unknown	No	2.2	2.2
6	IV (skin + liver)	N/A	No	Pneumonia	No	2.3	2.3
7	No	N/A	No	Pulmonary embolus	No	0.5	0.5
8	I (skin)	No	Relapse AML	Relapse	No	2.8	4.0
9	II (skin + gut)	Yes	Persistent CLL	Disseminated aspergillosis	No	4.5	4.5
10	No	No	Persistent CLL / Relapse MDS	Relapse	No	1.0	6.2
11	IV (skin + gut)	yes	No	Progressive multifocal leukoencephalopathy	No	8.2	8.2
12	II (gut)	Yes	No	Alive	No	>143.6	>143.6
13	II (skin + gut)	No	No	Pneumonia	No	3.7	3.7
14	I (skin)	No	Relapse CLL / Relapse MDS	Relapse	No	104.4	178.4
15	III (skin, gut, liver)	N/A	Persistent FL	Relapse	Yes	1.0	4.3
16	II (gut)	yes	No	Alive	Yes	>185.0	>185.0
17	No	No	Relapse MDS	Relapse	Yes	7.6	10.1
18	N/A	N/A	No	Septicemia	Yes	0.3	0.3
19	II(skin, gut, liver) hyperacute	Yes	No	Pneumonia	Yes	25.8	25.8
20	II (skin + gut)	Yes	No	Pneumonia	Yes	31.2	31.2
21	II (skin + gut)	Yes	Relapse DLBCL / Relapse MDS	Relapse	Yes	2.9	8.4

Abbreviations: AML= acute myeloid leukemia; CLL= chronic lymphocytic leukemia; COD= cause of death; DLBCL= diffuse large B-cell lymphoma; FL= follicular lymphoma; GVHD= graft-versus-host disease; MDS= myelodysplastic syndrome; ms= months; N/A= not applicable; OS= overall survival; RFS= relapse-free survival (expressed in months post-transplantation).