Hypomethylating Agent Induction Therapy Followed By Hematopoietic Cell Transplantation Is Feasible in Patients With Myelodysplastic Syndromes

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Abstract: Disease remission in patients with myelodysplastic syndromes can be achieved with azanucleosides, which act as pyrimidine analogs and hypomethylating agents. However, despite treatment with azanucleoside induction, patients with myelodysplastic syndromes nearly always relapse. Allogeneic hematopoietic cell transplantation (HCT) can be curative, but it is risky. Given that azanucleosides affect human leukocyte antigen expression and lymphocyte reactivity, we conducted a retrospective study to define the impact of pre-HCT azanucleoside therapy on post-HCT donor chimerism. Patients receiving azanucleoside induction therapy achieved rapid and high levels of donor chimerism post-transplant. Lineage analysis also found rapid donor chimerism of lymphocyte and granulocyte subsets. These data indicate the feasibility of pretransplant azanucleoside therapy in patients who subsequently receive an HCT.

Introduction

Recently, several new therapies have become available to treat patients with myelodysplastic syndromes (MDS). Azanucleosides such as azacitidine (Vidaza, Celgene) and decitabine (Dacogen, Eisai), which exhibit dual properties as pyrimidine analogs and hypomethylating agents, change the natural history of MDS, reduce transfusion requirements, extend survival, and delay progression to acute leukemia.[1-5] Despite improvements in clinical outcomes with azanucleoside treatment, nearly all MDS patients suffer from disease relapse and progression. Thus, the only potentially curative option for most patients with MDS is allogeneic hematopoietic cell transplantation (HCT).[6-10]

It is challenging to determine when to proceed to HCT in patients with MDS. In general, younger patients with lower burdens of MDS, fewer comorbidities, and less transfusion dependence

tend to achieve better post-transplant outcomes.[11-15] Early studies of pretransplant induction chemotherapy with cytotoxic agents in MDS patients found no clear post-transplant benefits.[13,16-21] In 2004, a decision model developed by Cutler and colleagues indicated a survival advantage with early HCT among patients classified as intermediate-2 and high-risk MDS based on International Prognostic Scoring System (IPSS) criteria.[22]

However, with the advent of hypomethylating azanucleosides, MDS patients can achieve disease remissions, transfusion independence, and improved performance status by way of novel epigenetic effects.[1,4,5] In current practice, most intermediate-2 and high-risk MDS patients do not undergo early HCT; rather, they receive several cycles of azanucleoside induction therapy before proceeding to HCT, often to allow time to identify a suitable HCT donor. Preliminary reports indicate that pretransplant azanucleoside therapy is feasible[23,24]; however, no reports have described the impact of azanucleoside induction therapy on post-transplant donor chimerism. To begin to address this issue, we performed a retrospective study to analyze post-transplant outcomes in MDS patients who received hypomethylation before allogeneic HCT.

Materials and Methods

Patient and Disease Characteristics

Medical records of consecutive MDS patients who underwent HCT between 2003 and 2008 were retrospectively analyzed as part of an approved study by the University of Florida Institutional Review Board. The diagnosis of MDS was confirmed by hematopathologists at the University of Florida and Shands Hospital (both in Gainesville, FL).

Patients were treated with azanucleoside induction chemotherapy at the discretion of the treating physician. Indications for induction therapy included rapidly rising bone marrow blast percentage on 2 consecutive bone marrow biopsies at least 4 months apart. From 2003 to 2008, azanucleoside agents were used in intermediate-2 and high-risk MDS patients (based on IPSS criteria) who required blood transfusions for symptomatic cytopenias or antimicrobials for frequent infections. We report the clinical and laboratory outcomes of all consecutive MDS patients at our institution who (1) received hypomethylating agent therapy and (2) subsequently received an allogeneic HCT.

Induction Chemotherapy

Induction therapy consisted of either azacitidine at 75 mg/m^2/day intravenously (IV) or subcutaneously on days 1–7, or decitabine at 20 mg/m^2/day IV on days 1–5. No patients crossed over from one hypomethylating agent to another. Patients who received azanucleoside therapy continued with treatment until MDS relapse or progression, at which point they proceeded to allogeneic HCT. Two patients within the azanucleoside group developed rapidly progressing MDS immediately prior to HCT and therefore received high-intensity induction chemotherapy, such as a fludarabine, cytarabine, and filgrastim (FLAG) regimen (consisting of fludarabine 30 mg/m^2/day IV on days 1–5, cytarabine 2,000 mg/m^2/day IV on days 1–5, and granulocyte colony-stimulating factor 400 µg/m^2/day from day 0 until the achievement of an absolute neutrophil count >500 cells/µL) and/or a 7+3 regimen (consisting of cytarabine 100 mg/m^2/day continuous IV on days 1–7 and idarubicin 12 mg/m^2/day IV on days 1–3).

Transplantation Regimens

DNA-based human leukocyte antigen (HLA) typing of the donor and recipient was performed for HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1. High-resolution typing for HLA-DRB1 was performed in all patients; high-resolution typing for HLA-A, HLA-B, and HLA-C was performed in patients who received a transplant after June 2005. Myeloablative conditioning regimens were used in patients younger than 60 years who did not have severe comorbidities. The myeloablative regimen consisted of cyclophosphamide (total dose of 120 mg/kg over 2 days) and total body irradiation (total dose of 1,350 cGy in 9 fractions).

Reduced-intensity conditioning regimens were used in patients older than 60 years and in patients with comorbidities that confer a higher risk of post-transplant morbidity and mortality. These regimens included fludarabine (total dose of 150 mg/m^2 given over 5 days), busulfan (total dose of 8 mg/kg orally or 6.4 mg/kg IV given over 4 days), and rabbit anti-thymocyte globulin ([ATG] total dose of 6 mg/kg given over 4 days); or fludarabine (total dose of 120 mg/m^2 given over 4 days), melphalan (total dose of 140 mg/m^2 given once) and, if the donor was unrelated, rabbit ATG (total dose of 12 mg/kg given over 4 days).

Allogeneic HCT grafts were infused on day 0. Graft sources included matched-related donor mobilized peripheral blood stem cells (n=3), matched unrelated donor mobilized peripheral blood stem cells (n=2), and umbilical cord blood (UCB) cells (n=3). One matched unrelated donor HCT patient received a single-locus allele HLA-mismatched transplant. All UCB HCT patients received a 4 out of 6 HLA-matched transplant. One of 3 UCB HCT patients received pooled, double UCB transplants. Graft versus host disease (GVHD) prophylaxis included cyclosporine or tacrolimus, combined with methotrexate.

Laboratory Measures

The absolute lymphocyte count was determined at a pre-admission visit before the planned HCT. Donor chimerism in peripheral blood was measured by standard automated short tandem repeat analysis (Applied Biosystems) of the donor and of the patient before and after transplant. Mean percentages of 9 loci at days 30, 60, and 100 reflect the proportion of circulating donor granulocytes, T lymphocytes, and B lymphocytes that were separated by magnetic beads coated with appropriate monoclonal antibodies. Mean percentages of donor chimerism between the 2 induction therapy groups were reported at 30, 60, and 100 days after the transplant.

Statistical Analysis

All patients provided written informed consent and were treated according to protocols approved by the University of Florida Institutional Review Board. Data were analyzed as of June 8, 2009. Survival curves were calculated according to the Kaplan-Meier method and compared by the 2-sided log-rank test.[25,26]

Results

Patient Population

Between 2003 and 2008, 8 MDS patients received azanucleoside induction therapy prior to HCT at the University of Florida (Table 1). Patients received a median of 8 cycles (range, 2–14) of single-agent therapy. Four patients received azacitidine, and 4 patients received decitabine. All patients had excess blasts at diagnosis (Table 2). Two of the azacitidine patients developed rapidly progressive disease, which was subsequently treated with high-intensity induction chemotherapy (the FLAG regimen or the 7+3 regimen). Among the 8 patients, 4 presented at transplant with more advanced disease. Given the older age (median, 60.5 years; range, 53–66 years) and decreased performance status of the MDS patients, nonmyeloablative regimens were used more often (75%). The older age of these patients also meant that most of them lacked living matched siblings, and therefore unrelated HCT donors were used in 62.5% of transplants. ATG was used in conditioning all but 1 patient.

Engraftment

After the transplant, the time to neutrophil engraftment (absolute neutrophil count ≥500 cells/μL for 3 days or ≥1,500 cells/μL for 1 day) was 19 days. Six months after the transplant, 4 of 8 patients achieved platelet engraftment of platelets at or exceeding 100,000/mm^3 untransfused.

Table 1. Patient Characteristics

Characteristic	Azanucleoside Induction Pre-transplant (N=8)
Age, years (median range)	60.5 (53–66)
Sex	
• Male	5
• Female	3
Disease at diagnosis	
• RAEB-1	7
• RAEB-2	1
Induction regimens before HCT	
• Azacitidine (Vidaza)	4
• Decitabine (Dacogen)	4
• FLAG	2
Azanucleoside cycles	
• Median	8
• Range	2–14
Disease at HCT	
• CR	2
• RAEB-1	3
• RAEB-2	3
BM blasts at HCT	9% ± 2%*
Time from diagnosis to HCT (days)	411 ± 86
Karnofsky performance status at HCT	80% ± 4%
Transfusion dependent at HCT	75% ± 16%
Absolute lymphocyte count before HCT	806 ± 180
Conditioning regimen	
• Myeloablative	2 (25%)
• RIC	6 (75%)
• ATG	7 (88%)
Donor sources	
• MRD	3 (38%)
• MUD	2 (25%)
• UCB	3 (38%)
Follow-up, days (median, range)	232.5 (33–2161)

*Plus-minus values are mean ± standard error of the mean.

ATG=anti-thymocyte globulin; BM=bone marrow; CR=complete remission; FLAG=fludarabine, cytarabine, and filgrastim; HCT=hematopoietic cell transplantation; MRD=adult matched-related donor; MUD=adult matched unrelated donor; RAEB-1=refractory anemia with excess blasts 5-10%; RAEB-2=refractory anemia with excess blasts 11–20%; RCMD=refractory cytopenia with multilineage dysplasia; RIC=reduced intensity conditioning; SEM=standard error of the mean; UCB=umbilical cord blood.

Table 2. Patient Outcomes

Patient	Age/Sex	MDS at Dx	Induction	Days From Dx to HCT	MDS at HCT	Conditioning	Donor/ Graft	Relapse, Day	Death, Day	Acute GVHD	Chronic GVHD
UPN1	63/ Male	RAEB-1	Decitabine	168	RAEB-2	Flu/Bu/ATG	MRD PBSC	No	No	Grade 3	Extensive
UPN2	66/ Male	RAEB-1	Azacitidine	196	RAEB-1	Flu/Bu/ATG	UCB	Yes, 31	Yes, 116	Grade 4	N/A
UPN3	53/ Male	RAEB-1	Azacitidine	147	RAEB-1	Cy/TBI/ATG	UCB	No	Yes, 33	No	N/A
UPN4	64/ Female	RAEB-2	Azacitidine, FLAG, 7+3	455	CR	Flu/Mel/ATG	Pooled UCB	Yes, 176	Yes, 242	No	No
UPN5	60/ Female	RAEB-1	Decitabine	308	RAEB-1	Flu/Bu/ATG	MUD PBSC	Yes, 99	Yes, 383	Grade 3	Extensive
UPN6	59/ Male	RAEB-1	Decitabine	560	RAEB-2	Flu/Bu/ATG	MRD PBSC	No	No	No	No
UPN7	54/ Male	RAEB-1	Decitabine	784	CR	Cy/TBI	MUD PBSC	No	Yes, 163	Grade 2	No
UPN8	62/ Female	RAEB-1	Azacitidine, FLAG	672	RAEB-2	Flu/Bu/ATG	MRD PBSC	Yes, 140	No	No	No

ATG=anti-thymocyte globulin; Bu=busulfan; CR=complete remission; Cy=cyclophosphamide; Dx=diagnosis; FLAG=fludarabine, cytarabine, and filgrastim; flu=fludarabine; GVHD=graft-versus-host disease; HCT= hematopoietic cell transplantation; MDS=myelodysplastic syndromes; MEL=melphalan; MRD=adult matched-related donor; MUD=adult matched unrelated donor; N/A=not applicable; PBSC=peripheral blood stem cells; RAEB-1=refractory anemia with excess blasts 5–10%; RAEB-2=refractory anemia with excess blasts 11–20%; TBI=total body irradiation; UCB=umbilical cord blood; UPN=unique patient number.

Rapid Donor Chimerism in the Azanucleoside Induction Group

Donor chimerism of granulocytes, T lymphocytes, and B lymphocytes was measured in peripheral blood at days 30, 60, and 100. The mean percentages of donor cells according to the leukocyte group were plotted against time (Figure 1). The grouped mean percentage of donor chimerism (average percent of granulocyte, T lymphocyte, and B lymphocyte chimerism) increased rapidly at day 30 and remained elevated at days 60 and 100 (Figure 1A). Specifically, patients achieved high levels of the mean percentage of donor chimerism at day 30 (93%), day 60 (95%), and day 100 (97%). Analysis of the T lymphocyte subset post-transplant showed that these patients achieved rapid donor T lymphocyte chimerism at day 30 (83%), day 60 (90%), and day 100 (96%; Figure 1B). Donor B lymphocyte chimerism was also rapid at day 30 (93%), day 60 (90%), and day 100 (96%; Figure 1C). Finally, granulocyte chimerism also rose rapidly post-transplant at day 30 (100%), day 60 (97%), and day 100 (98%; Figure 1D).

Post-transplant Clinical Outcomes in the Azanucleoside Induction Group

At median follow-up of 11.5 months (range, 1–137 months), 4 of 8 patients developed grades 2–4 acute GVHD, and 3 of 8 patients developed grades 3–4 acute GVHD. Chronic GVHD developed in 2 of 8 patients, with both cases progressing to an extensive stage. The cumulative risk of relapse at 5 years was 48 (Figure 2). Of those patients with relapsed disease, the median time to relapse was 120 days (range, 31–176 days).

Donor leukocytes were infused in 2 relapsing patients, both of whom achieved complete remission in their bone marrow. The most common causes of nonrelapse mortality included diffuse alveolar hemorrhage, acute GVHD, and chronic GVHD. For all patients, the median overall survival was 242 days, and the estimated 5-year survival was 42%, with a plateau for surviving patients (Figure 3).

Discussion

Currently, it is common practice for hematologists/oncologists to administer azanucleoside induction therapy to

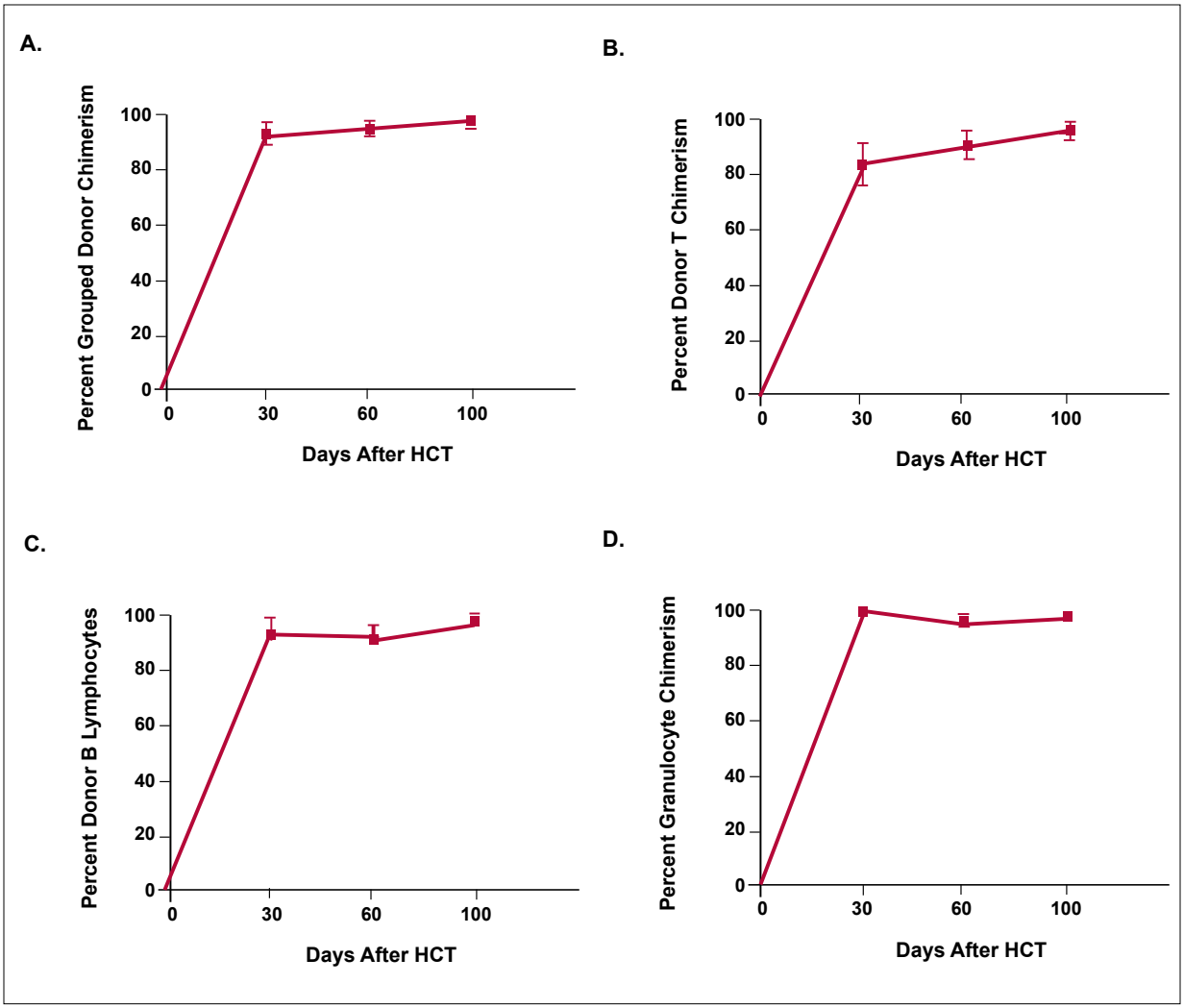

Figure 1. Donor chimerism after hematopoietic cell transplantation (HCT) in patients with myelodysplastic syndromes who have a history of pre-HCT azanucleoside therapy. Donor chimerism of nucleated cells was measured in peripheral blood by short tandem repeat analysis. (A) Grouped donor chimerism was calculated by averaging the mean percentage of granulocyte, T lymphocyte, and B lymphocyte donor chimerism. Patients who received azanucleoside therapy prior to HCT achieved rapid and high levels of grouped donor chimerism. Subset analyses of (B) T lymphocytes, (C) B lymphocytes, and (D) granulocytes post-transplant revealed rapid donor chimerism at days 30, 60, and 100.

patients with MDS prior to HCT. However, feasibility data are lacking. The primary aim of this study was to evaluate the feasibility of administering azanucleoside induction therapy (azacitidine or decitabine) to MDS patients before HCT.

In particular, this report is the first to describe the effects of pretransplant azanucleoside induction therapy on post-HCT donor chimerism. Our cohort of MDS patients achieved rapid donor chimerism of all nucleated cells at days 30, 60, and 100. Subset analyses identified T lymphocytes, B lymphocytes, and granulocytes as responsible for this early donor chimerism. It is important to note that in our study, MDS patients who received pretransplant azanucleosides presented with decreased absolute lymphocyte counts, which is likely due to the repeated azanucleoside cytotoxic chemotherapy cycles used in older patients. Consequently, increased immunosuppression at HCT possibly permitted greater opportunity for donor hematopoietic stem and progenitor cell engraftment. Additionally, most of the MDS patients in our study received ATG as part of the transplant preparative regimen. ATG immunosuppression may also have impaired host alloreactivity, permitting rapid donor engraftment.

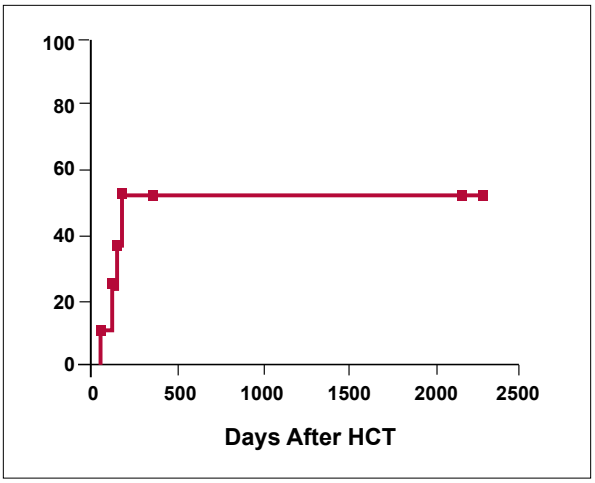

Figure 2. Incidence of relapse after allogeneic hematopoietic cell transplantation (HCT) in patients with myelodysplastic syndromes who are receiving pre-HCT azanucleosides.

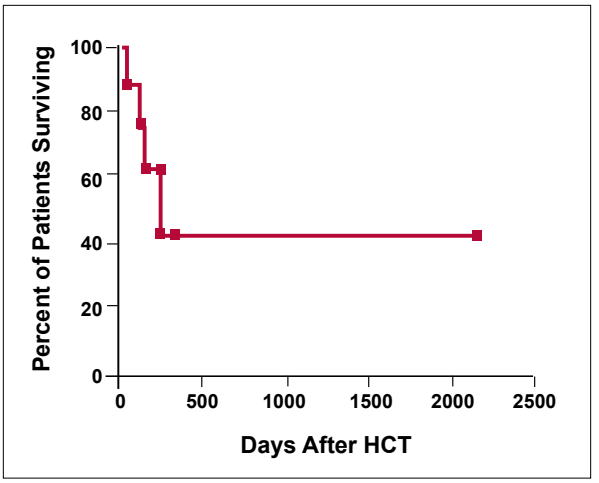

Figure 3. Overall survival after allogeneic hematopoietic cell transplantation (HCT) in patients with myelodysplastic syndromes who have a history of receiving azanucleoside therapy.

The MDS patient characteristics in this study represent a trend in clinical practice of using azanucleoside agents before proceeding to HCT. The potential benefits of administering hypomethylation for several months prior to HCT allows for more time to seek a best-matched donor, to decrease MDS disease burden, and to improve patient comorbidities and performance status. However, as demonstrated in our azanucleoside group, most of our MDS patients declined to undergo HCT until their disease progressed, and they subsequently underwent HCT with advanced disease burden. For this reason, it is not surprising that there was a higher relapse rate in our study group as compared with other studies that have reported transplant outcomes of lower-risk MDS patients.[23,24] Our observed relapses may reflect the progressive nature of chemotherapy-insensitive disease in patients whom we brought to transplant. Increased disease relapse may also be related to the use of ATG in the reduced-intensity conditioning regimen for these patients.[27]

Data from this study begin to define the impact of using azanucleoside agents in patients who subsequently undergo allogeneic HCT for MDS. Our results demonstrate the feasibility of azanucleoside induction therapy before allogeneic HCT and show rapid donor chimerism post-transplant. Larger studies with longer follow-up periods are needed to fully define the long-term effects of hypomethylating induction therapy on post-transplant chimerism and clinical outcomes.

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