Frequency of Allogeneic Hematopoietic Cell Transplantation Among Patients With High- or Intermediate-Risk Acute Myeloid Leukemia in First Complete Remission

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ABSTRACT

Purpose

To determine the frequency of allogeneic hematopoietic cell transplantation (HCT) for patients with acute myeloid leukemia (AML) in first complete remission (CR1).

Patients and Methods

Between January 1, 2008, and March 1, 2011, 212 newly diagnosed patients with AML received treatment at our center. Ninety-five patients age less than 75 years with intermediate- or high-risk AML achieved a complete remission, and 21 patients achieved a morphologic remission with incomplete blood count recovery.

Results

Seventy-eight (67%; 95% CI, 58% to 76%) of 116 patients received HCT at a median of 2.8 months (range, 0.5 to 19 months) from their CR1 date. The median age was 57 years in both the HCT patient group (range, 18 to 75 years) and the non-HCT patient group (range, 24 to 70 years; $P = .514$). Between the HCT patients and the non-HCT patients, the mean Eastern Cooperative Oncology Group performance status was 1.1 compared with 1.5, respectively ($P = .005$), and the average HCT comorbidity score within 60 days of CR1 was 1.7 and 2.1, respectively ($P = .68$). Twenty-nine (76%) of 38 non-HCT patients were HLA typed, and matched donors were found for 13 of these 29 patients (34% of all non-HCT patients). The most common causes for patients not receiving transplantation in CR1 were early relapse (within 6 months) in 12 patients (32%), poor performance status in eight patients (21%), and physician decision in five patients (13%).

Conclusion

HCT can be performed in CR1 in the majority of patients with AML for whom it is currently recommended. The main barriers to HCT were early relapse and poor performance status, highlighting the need for improved therapies for patients with AML of all ages.

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INTRODUCTION

Despite advances in therapy for the treatment of acute myeloid leukemia (AML), controversy remains regarding the efficacy of immediate allogeneic hematopoietic cell transplantation (HCT), particularly for patients with AML in first complete remission (CR1). Meta-analyses have been performed, where various trials assigned adults with AML in CR1 to undergo allogeneic HCT from an HLA-identical related donor versus alternative treatments and compared outcomes in patients according to

donor status. Although such donor versus no donor analyses are themselves subject to potential bias,¹ results suggest that allogeneic HCT offers a statistically significant advantage with regard to overall survival (OS), disease-free survival (DFS), and quality of life compared with chemotherapy or autologous HCT in some settings.²⁻⁴ In particular, this benefit is most apparent for patients with high-risk disease, perhaps less impressive for patients with intermediate-risk disease, and absent for patients with favorable-risk disease.^{2,3,5,6} Accordingly, consensus exists that patients with intermediate- or

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high-risk disease should receive HCT in CR1 if they have a matched related donor, with OS and DFS at 5 and 10 years after myeloablative allogeneic HCT exceeding 50% in some reports.^{7,8,9}

Unfortunately, less than 30% of adults will have an HLA-matched sibling donor. However, recent data suggest that outcomes after allogeneic HCT from fully matched unrelated donors seem to be similar to those after matched related donor transplantation.¹⁰⁻¹² Depending on ethnicity, matched unrelated donors can be found for 25% to 50% of patients who do not have a matched related donor. Additional data show that for patients age less than 45 years, outcomes after double cord transplantation are similar to those seen with either matched related donor or matched unrelated donor transplantation.^{13,14} Given the current criteria for cord blood transplantations based on cell dose and degree of mismatch, double cord blood should be available for approximately 95% of patients lacking a matched related or matched unrelated donor. In addition, HCT approaches using haploidentical family members have become increasingly successful.^{15,16} Therefore, alternative donors should be theoretically available for the large majority of patients with high-risk AML who do not have a matched sibling donor. Further broadening of transplantation applicability has resulted from reduced-intensity conditioning, which has become accepted as a means to extend HCT to older patients at the Fred Hutchinson Cancer Research Center (FHCRC) and at many other centers, up to age 75 years.

Despite encouraging results from previous HCT studies in high-risk adult patients with AML in CR1, it remains unclear what proportion of patients age less than 75 years whose risk of relapse would justify transplantation actually receive HCT. This is particularly the case in patients age 50 to 75 years, as suggested in a previous report from Estey et al.¹⁷ However, since that report, HCT has become more generally accepted and alternative donors have become more available. Therefore, we have re-examined the frequency of HCT among patients with AML who entered complete remission (CR) after receiving induction therapy at FHCRC, specifically those patients who were age less than 75 years, did not have favorable cytogenetics, and were not *NPM* positive/*FLT3* negative.

PATIENTS AND METHODS

Study Cohort

Consecutive patients older than age 18 years who presented to the University of Washington and FHCRC between January 1, 2008, and March 1, 2011, with untreated AML who achieved a first remission after induction chemotherapy were identified from our computerized database and included in this study. Patients were excluded if they did not achieve a morphologic remission or presented to our center after relapse. All patients who were treated on an investigational study signed a consent form approved by the Human Subjects Committee of the University of Washington and the Institutional Review Board of the FHCRC in accordance with the Declaration of Helsinki. In addition, separate institutional approval was obtained to retrospectively gather data from patient records and databases.

Study Variables

The specific baseline variables evaluated included the following: patient age; Eastern Cooperative Oncology Group (ECOG) performance status (PS) at the time of transplantation; HCT comorbidity index (HCT-CI); cytogenetics; secondary AML; HLA typing; number of chemotherapy cycles to achieve CR1; time from CR1 to HCT; number of consolidation courses; WBC, hemoglobin, and platelet counts at presentation and at HCT; presence of early relapse (within 6 months of CR1); previous consolidation chemotherapy;

disease status at HCT; and donor availability as defined by those CR1 patients who had an appropriate potential allogeneic stem-cell source identified and ready for use at the desired time for HCT. Donor searches initially investigated all relevant siblings; if a suitable fully matched family donor was not identified or readily available, an unrelated search was routinely undertaken. In general, potential appropriate cord blood units and/or haploidentical family members were only identified in the absence of either a matched related or unrelated donor. Treatment response criteria were used as proposed by the International Working Group for therapeutic trials in AML and further refined by the European LeukemiaNet.^{18,19} Cytogenetic aberrations to define AML risk were defined according to the 2008 WHO criteria and the European LeukemiaNet.^{19,20} The HCT-CI was calculated as described previously.^{21,22} The outcome variable was the frequency of HCT.

Statistical Methods

The objective of the study was to determine the frequency of allogeneic HCT among patients with AML in CR1, focusing on patients whom consensus would regard as appropriate candidates, as described in the previous section. Univariable logistic regression was used in an attempt to identify factors that were significantly different between the patients who received HCT and the patients who did not receive HCT.

RESULTS

Patient Characteristics

Between January 1, 2008, and March 1, 2011, 287 patients presented to our center with newly diagnosed, untreated AML. Of these patients, 53 were not treated at our center, seven were lost to follow-up, and 15 died within the first 30 days of induction, leaving 212 patients who completed induction chemotherapy (Fig 1). Patients who were treated and achieved CR1 received therapy using a variety of investigational studies or using standard induction regimens such as 7+3, cytarabine, and an anthracycline (idarubicin or daunorubicin). We excluded patients older than age 75 years and patients with favorable-risk disease [inversion 16, t(8,21), t(15;17), or *NPM1* positive/*FLT3* negative with normal cytogenetics] because HCT is generally not recommended in CR1 for such patients, leaving 116 patients with high- or intermediate-risk AML who obtained CR1. Of the 44 patients who did not obtain a CR, 10 received HCT on experimental protocols using radiolabeled antibodies or other novel approaches. Among the patients achieving morphologic remission (< 5% blasts by morphology), 95 patients (82%) had peripheral-blood counts that met criteria for CR, whereas 21 patients (18%) had incomplete blood count recovery (platelet count < 100,000/ μ L or absolute neutrophil count > 1,000/ μ L) and were thus classified as CRi at time of HCT.¹⁹ Sixty-six (69%) of 95 patients who met the criteria for CR underwent HCT, whereas 13 (62%) of 21 patients who achieved a CRi underwent HCT. The characteristics of the study population are listed in Table 1.

Transplantation Characteristics Among Non-HCT Patients and Those Receiving HCT in CR1

Seventy-eight (67%; 95% CI, 58% to 76%) of 116 patients who achieved a morphologic remission received HCT at a median of 2.8 months (range, 0.5 to 19 months) from their remission date. Patients who received HCT had a better PS at time of morphologic remission ($P = .005$) and were less likely to have experienced relapse (> 5% blasts) within 6 months of morphologic remission, when compared with patients who did not receive HCT. The average ECOG PS was 1.1 in the group who received HCT compared with 1.5 among the patients who did not undergo HCT ($P = .005$). Seventy-three (94%) of

Fig 1. Schematic representation of the 287 newly diagnosed patients with acute myeloid leukemia (AML) seen at our center between January 1, 2008, and March 1, 2011. CR, complete remission; HCT, hematopoietic cell transplantation.

78 patients had an ECOG PS of 1 among those who received HCT in CR1 compared with 28 (74%) of 38 patients who did not receive HCT ($P = .005$). In contrast, neither age nor HCT-CI score differed significantly between patients who did and did not receive HCT. The average HCT-CI score within 60 days of remission was 1.7 (range, 0 to 11) in the HCT group and 2.1 in the non-HCT group ($P = .68$).

Transplantation Characteristics and Survival of Patients Receiving HCT

Sixty-four (82%) of 78 patients who underwent HCT received hematopoietic stem cells from either a sibling donor or unrelated donor matched at HLA-A, HLA-B, HLA-C, and HLA-DR loci, with six patients (8%) receiving cells mismatched at a single antigen, one patient receiving a haploidentical related graft, and one patient receiving a dual-antigen/allele mismatched allograft (Table 2). Double umbilical cord blood HCT was performed in six patients (8%), with four of the six patients receiving single-antigen mismatched cords, one patient receiving two-antigen mismatched cords, and one patient receiving both a single-antigen and a two-antigen mismatched cord. Hematopoietic cells were derived from bone marrow in nine patients (11%) and peripheral blood mobilized with granulocyte colony-stimulating factor in 63 patients (81%). Of the 78 patients who received transplantation in CR1, 42 have died by last contact. The estimated survival rate at 4 years in this group was 44% (95% CI, 33% to 56%; Fig 2). Median follow-up among the 36 survivors is 3.0 years (range, 1.8 to 12.4 years).

Reasons for Failure to Receive HCT

Twenty-nine (76%) of 38 non-HCT patients were HLA typed, and matched donors were found for 13 (45%) of these 29 patients (five related and eight unrelated; Tables 3 and 4). Three (33%) of the nine nontyped patients had financial barriers preventing HCT, one patient (11%) experienced relapse before donor identification, and three other patients (33%) were thought to be unfit transplantation candidates as a result of poor PS or social/psychological factors (Table 3). Only two (5%) of these 38 patients received HCT beyond CR1, after achieving a second remission. The most common causes for patients not receiving transplantation in CR1 were early relapse (within 6 months; 12 patients; 32%), poor performance status (eight patients; 21%), or physician decision (five patients; 13%). Although 25 of the 38 patients who did not receive transplantation had no donor, this was

primarily because of the cessation of donor searches as a result of other patient factors, such as relapse or decline in performance status. The lack of an available donor was not the primary reason invoked for any of the 38 patients who did not receive an HCT in CR1 (Table 3).

Nineteen (50%) of 38 non-HCT patients experienced relapse after achievement of CR1, and the median time to relapse from CR1 was 120 days (range, 28 to 361 days). Twelve of these 19 relapses occurred before planned transplantation and were cited as the reason for no HCT. An additional five patients died (without confirmed evidence of relapse after CR1) after achievement of CR1 (deaths occurred at days 13, 65, 66, 360, and 446). Of these five patients, three patients were deemed unfit for HCT because of concurrent medical or social issues, one patient deferred transplantation as a result of personal preference, and one patient returned to Alaska for consolidation and was lost to follow-up. Four of these five patients died of unknown causes, whereas one patient presumably died of sepsis.

DISCUSSION

The data presented in this retrospective analysis suggest that HCT can be performed in CR1 in the majority of high- or intermediate-risk patients with AML for whom it is currently recommended at our center. Patients in whom HCT is not undertaken are characterized by a poorer PS (but not older age) and early relapse. This analysis included stem cells from all available donor sources including matched related and unrelated donors, haploidentical donors, and cord blood, providing a more accurate assessment of transplantation feasibility in the era of alternative stem-cell sources. This factor is important when considering the barriers to transplantation that can be modified or improved, now that donor availability is becoming less of an issue. Although we recognize that a donor may not have been found in each of the 25 patients in whom no donor was identified, the lack of a donor was not cited in any of the 38 patients who did not receive HCT, suggesting that the donor versus no donor rationale used in previous transplantation outcome trials may be currently much less relevant. Donor searches in this study were often discontinued for patients deemed ineligible for transplantation for other reasons, making it difficult to determine whether the lack of a donor would have been a factor for these patients. In fact, the main barrier to transplantation for our patients proved to be early relapse and poor PS, highlighting the

Table 1. Patient Characteristics

Characteristic	HCT (n = 78)		No HCT (n = 38)		P (from logistic regression)
	No. of Patients	%	No. of Patients	%	
Age, years					
Median	57		57		.514
Range	18-75		24-70		
ECOG performance status (at first CR/CRi)					.005
Mean	1.1		1.5		
Range	1-2		1-4		
0	0	0	0	0	
1	73	94	28	73	
2	5	6	4	11	
3	0	0	2	5	
4	0	0	4	11	
HCT-CI (within 60 days of CR/CRi)					.68
Mean	1.7		2.1		
Range	0-11		0-7		
Unfavorable cytogenetics (pretreatment)		24		18	.47
Secondary AML		49		39	.35
HLA typing performed	78	100	29	76	
Donor available	78	100	13	34	
> 1 cycle of chemotherapy to achieve first CR/CRi	34	44	18	47	
Time from first CR/CRi to HCT, months					
Median	2.8		NA		
Range	0.5-19				
No. of consolidation courses					
Median	1		2		
Range	0-4		0-4		
WBC at diagnosis, $\times 10^3/\mu\text{L}$					
Median	3.4		26		
Range	0.5-91.9		1.06-297		
Platelet count > 100,000/ μL at HCT	65	83	NA		
ANC > 1,000/ μL at HCT	73	94	NA		
Relapse ($\geq 5\%$ marrow myeloblasts or circulating peripheral myeloblasts)	22		19		
Within 3 months	9		8		
Between 3 and 6 months	5		2		
After 6 months	8		9		
Status at HCT or response (for no HCT)					
CR	48	62	22	57	
CR-MRD	17	22	8	21	
CRi	5	6	4	11	
CRi-MRD	8	10	4	11	

Abbreviations: AML, acute myeloid leukemia; ANC, absolute neutrophil count; CI, comorbidity index; CR, complete remission; CRi, morphologic remission with incomplete blood count recovery; ECOG, Eastern Cooperative Oncology Group; HCT, hematopoietic cell transplantation; MRD, minimal residual disease; NA, not applicable.

Table 2. Donor and Transplantation Characteristics of Patients Receiving HCT in Remission

Donor and Transplantation Characteristics	No. of Patients (n = 78)	%
Donor age, years		
Median	35	
Range	18-73	
Donor sex		
Male	34	
Female	38	
Cord	6	
Donor type		
Related (all 10/10 match except 1 haploidentical)	23	29
Unrelated	55	71
HLA matching		
10/10 match	64	82
Single-antigen mismatch (all unrelated)	6	8
Two-antigen mismatch unrelated	1	1
Haploidentical	1	1
DUCB*	6	8
Single-antigen mismatch in both cords	4	
Two-antigen mismatch in both cords	1	
Single-antigen/two-antigen mismatch	1	
Patient/donor sex		
Male/male	23	30
Female/female	17	21
Male/female	21	27
Female/male	11	14
Cord	6	8
Conditioning regimen		
Myeloablative	45	58
Nonmyeloablative	33	42
Stem-cell source		
Bone marrow	9	11
Peripheral blood	63	81
DUCB	6	8
Nucleated cell dose received, $\times 10^8$		
Bone marrow		
Cells per kilogram		
Median	2.32	
Range	0.93-6.5	
Cells total		
Median	165.6	
Range	82.7-388	
Peripheral blood		
Cells per kilogram		
Median	10.93	
Range	0.14-26.73	
Cells total		
Median	838.6	
Range	11.4-1,855.3	
DUCB		
Cells per kilogram		
Median	0.38	
Range	0.29-0.48	
Cells total		
Median	34.9	
Range	23.7-43.5	

Abbreviations: DUCB, double umbilical cord blood; HCT, hematopoietic cell transplantation.

*The six DUCB transplantations are only counted once among the total number of patients.

need for improved induction therapies for patients with AML of all ages. Additionally, the majority of patients who did not receive transplantation in first morphologic remission as a result of physician decision had intermediate-risk disease and were monitored closely in CR1.

Fig 2. Estimate of the probability of survival among the 79 patients who received hematopoietic cell transplantation (HCT) in first complete remission.

Our analysis reveals that patients who did not receive HCT were characterized by poorer PS, not older age. This finding highlights the improved feasibility of transplantation in older populations in the setting of reduced-intensity conditioning regimens. These data will serve as a platform to prospectively evaluate the feasibility of HCT in a large cohort of patients with AML in CR1 for whom transplantation would be recommended. Further evaluation of the barriers noted in our study (such as lack of financial support, early relapse or death, patient wish, and physician decision) will determine whether these factors can be altered to increase access to HCT and in turn improve survival.

The feasibility of allogeneic HCT was addressed in one prior prospective study from the MD Anderson Cancer Center, which included all untreated patients with AML age ≥ 50 years.¹⁷ Ninety-nine (38%) of 259 patients achieved CR, and of those 99 patients, only 53 (54%) were seen by the transplantation service for a consult. The reasons for not referring the remaining 46 patients were unclear in almost half ($n = 21$). Among the 53 patients referred to HCT, suitable HLA-matched donors were found for 26 patients (21 siblings, five unrelated donors), and 14 patients actually underwent HCT (13 from sibling donors). Among those who received a consult, the lack of available sibling donors was cited in 60% of patients as the main barrier to transplantation. The authors attempted to find one or more

Table 4. Donors Identified for Patients Who Were HLA Typed But Did Not Receive HCT

Donor Identified	No. of Patients With No HCT (n = 38)
MRD	5
MUD	6
DUCB	2

Abbreviations: DUCB, double umbilical cord blood; HCT, hematopoietic cell transplantation; MRD, matched related donor; MUD, matched unrelated donor.

chemotherapy pair-mates for each patient who underwent HCT based on cytogenetics, age, and lead-time bias. On the basis of this comparison, there was a more than 99% probability that the outcome after HCT was superior to that seen in patients who did not receive transplantation. However, the 14 patients who underwent HCT represented only 26% of those seen by the transplantation service, only 14% of all those who achieved a CR, and only 5% of the original 259 patients entered onto the study. This study did not examine the role of comorbidities or organ function in transplantation decision making and was performed before the general acceptance of unrelated and alternative donors. To this end, a German AML Intergroup prospective study showed a 61% transplantation rate among younger patients with high-risk AML deemed eligible. Notably, however, the oldest patient who received a transplantation on trial was 62 years old, and only 7% of these patients received grafts from alternative donor sources such as cord blood or haploidentical donors.²³

It has been previously accepted that only fit patients were referred for unrelated donor transplantations when a matched sibling donor was not readily available; however, those patients perceived to be at highest relapse risk might be referred for HCT using an alternative donor stem-cell source. In addition, there may have been a general reluctance to refer patients for allogeneic HCT. At least two major reasons might account for this: high-risk patients and their physicians may significantly overestimate the benefits of conventional chemotherapy alone, and many nontransplantation physicians may overestimate the morbidity of the HCT. Along these lines, it remains worth noting that day 100 nonrelapse mortality in many studies using reduced-intensity conditioning has been shown to be $\leq 10\%$ and overall nonrelapse mortality is not higher than 20%, whereas cure rates may be up to 50% (compared with 10% after chemotherapy alone in high-risk patients).⁹

It clearly takes time and resources to identify potential donors, and there are no prospective data addressing how often this can actually be done. Although one can reasonably expect that figure to increase with increasing acceptance of HCT for high-risk disease, it remains a question of whether alternative donors can be found rapidly enough to treat those without matched family members. We are not aware of any published prospective studies evaluating the outcome of alternative donor transplantations for a large cohort of adult patients with high-risk AML that allows for an estimation of the impact of HCT on eventual survival. Thus, the Southwest Oncology Group hypothesis in the upcoming S1203 trial is that at least 60% of adults age less than 65 years with high-risk AML in first CR can be treated with an allogeneic transplantation using matched or haploidentical family members, unrelated donors, or cord blood as the donor source (<http://clinicaltrials.gov/ct2/show/NCT01802333?term=SWOG+1203&rank=1>). The Southwest Oncology Group study S1203 randomly

Table 3. Reasons for No HCT

Reasons for No HCT	No. of Patients			
	No HCT (n = 38)	HLA Typed (n = 29)	No HLA Typing (n = 9)	Donor Available (n = 13)
Early relapse	12	11	1	6
Comorbidities/poor performance status	8	7	1	3
Financial	4	1	3	0
Physician decision	5	4	1	1
Patient wish	2	2	0	1
Lost to follow-up	3	2	1	1
Social/psychiatric factor	4	2	2	1

Abbreviation: HCT, hematopoietic cell transplantation.

assigns patients age 15 to 65 years with newly diagnosed AML to induction with either 7 + 3 or idarubicin/high-dose cytarabine $\pm$ vorinostat. All enrolled patients are HLA typed, and those with high-risk AML receive an automatic transplantation consult. By performing transplantation in 60% of adults with high-risk AML in CR1 and achieving a 44% DFS at 2 years, OS can improve at 2 years for all high-risk patients from the historic level of 22% to at least 35%. For patients with AML who do not receive transplantation, barriers to transplantation will be chronicled and critically assessed. We anticipate that prospective evaluation of the feasibility and access to HCT will help address the obstacles preventing successful outcomes, broaden the future applicability of this procedure, and ultimately improve survival.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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