Impact of hematopoietic chimerism at day +14 on engraftment after unrelated donor umbilical cord blood transplantation for hematologic malignancies

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ABSTRACT

Background

Cord blood transplant is a feasible treatment alternative for adult patients with hematologic malignancies lacking a suitable HLA-matched donor. However, the kinetics of myeloid recovery is slow, and primary graft failure cannot be detected easily early after transplantation. We investigated the impact of hematopoietic chimerism status from unselected marrow cells 14 days after transplantation on predicting engraftment after a cord blood transplant.

Design and Methods

Seventy-one adult patients with hematologic malignancies undergoing single-unit unrelated donor cord blood transplantation after a myeloablative conditioning regimen were included in the study. All patients received conditioning regimens based on busulfan, thiotepa and antithymocyte globulin. Chimerism status was assessed analyzing short tandem repeat polymorphisms.

Results

The cumulative incidence of myeloid engraftment at 1 month was significantly lower in patients with mixed chimerism than in those with complete donor chimerism (55% *vs.* 94%; $p<0.0001$). For patients achieving myeloid recovery, the median time of engraftment was 16 days when donor chimerism at day + 14 was higher than 90%, compared with 24 days when donor chimerism was below this level ($p<0.001$). A donor chimerism level of 65% was found to be the best cut-off point for predicting primary graft failure, with a sensitivity of 97% and a specificity of 80%. The incidence of primary graft failure was 67% for patients with less than 65% donor chimerism at day +14 as compared to only 2% for those with more than 65% donor chimerism ($p<0.001$). Patients with mixed chimerism also had a lower cumulative incidence of platelet engraftment than those with complete chimerism (62% *vs.* 89%; $p=0.01$).

Conclusions

Donor-recipient chimerism status at day +14 predicts engraftment after a single-unit cord blood transplant in adults.

Key words: hematopoietic chimerism, graft failure, engraftment, cord blood transplantation.

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Introduction

Cord blood transplantation (CBT) has emerged recently as an attractive alternative for the treatment of high-risk adult patients with hematologic malignancies.[1-6] Although the procedure is feasible, the kinetics of engraftment remains one of the most important concerns after CBT for adult patients. Primary graft failure and delayed engraftment are both potential threats that cannot be predicted with ease, early after CBT. Some pretransplant characteristics, mainly the cell dose infused, have been related to engraftment.[7-11] However, once the transplant is ongoing, additional tools providing information about engraftment outcome are required.

Short tandem repeat (STR) polymorphisms allow the study of molecularly mixed chimerism after hematopoietic stem cell transplantation (HSCT), even in cases involving a low number of cells.[12] In this regard, hematopoietic chimerism status has been related to engraftment in other transplant settings,[13-19] and its early assessment could be useful in predicting delayed engraftment and primary graft failure after CBT.

This study aimed to analyze the predictive value of assessing chimerism soon after CBT for the outcome of myeloid and platelet engraftment in adult patients.

Design and Methods

Inclusion criteria

From June 2000 to March 2007, 71 adult patients with hematologic malignancies undergoing single-unit unrelated donor CBT after a myeloablative conditioning regimen were included in the study. DNA from unmanipulated bone marrow cells was obtained from all patients 14 days after the transplant. The research was approved by the ethics committee and written informed consent was obtained from all patients.

Transplant procedures

All patients received conditioning regimens based on busulfan, thiotepa and antithymocyte globulin (ATG). During the study period, four schedules were used. (i) Nine patients received thiotepa at a dose of 10 mg/kg (days -9 and -8 before the transplant), oral busulfan at a dose of 12 mg/kg (days -7 to -4), cyclophosphamide at a dose of 120 mg/kg (days -4 and-3) and horse ATG at a dose of 60 mg/kg (days -5 to -2). (ii) Seven patients received the same schedule using rabbit ATG at a dose of 8 mg/kg (days -5 to -2). (iii) Twenty-six patients received the same schedule but using intravenous busulfan at a dose of 9.6 mg/kg and rabbit ATG 8 mg/kg; (iv) Twenty-nine patients received thiotepa 10 mg/kg (days -7 and -6), intravenous busulfan 9.6 mg/kg (days -5 to -3), fludarabine 150 mg/m^2 (days -5 to -3) and rabbit ATG 8 mg/kg (days -5 to -2). Graft-versus-host disease (GVHD) prophylaxis was carried out in all cases with cyclosporine and prednisone. All patients received granulocyte colony-stimulating factor from day 7 after the transplant until engraftment.

The infused cord blood unit had to fulfill the following two criteria at cryopreservation: (i) total nucleated cell content greater than 1×10^7/kg of recipient's body weight; (ii) donor–recipient HLA matching greater than 3/6, considering HLA-A and -B by serological techniques or low-resolution DNA and DRB1 by high-resolution DNA techniques.

Polymerase chain reaction amplification of short tandem repeat markers

To establish the pretransplant STR marker profile for each donor–recipient pair, DNA was isolated from each patient's peripheral blood and from umbilical cord blood unit samples using a standard salting-out procedure. Hematopoietic chimerism was analyzed in unmanipulated bone marrow specimens collected 14 days after the transplant. Bone marrow DNA was isolated with the QIAmp Blood Kit (QIAGEN, Hilden, Germany). After extraction, DNA was eluted to a concentration of 0.125 ng/μL in 10 μL of TE buffer. STR markers were amplified using the AmpFSTR SGM plus kit (Applied Biosystems). The polymerase chain reaction was set up in a final volume of 25 μL using a Mastercycler personal thermocycler (Eppendorf, Hamburg, Germany). Amplified products were analyzed on an ABI Prism 310 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA). The collected data were analyzed with GeneScan software, and automating genotyping of alleles was performed with Genotyper software (Applied Biosystems). Mixed chimerism was quantified from the ratio of the peak area of each donor and recipient informative allele.[12] The final proportion of donor chimerism was obtained by averaging the results of all informative individual alleles.

Definitions

Myeloid engraftment was defined as the first day of a neutrophil count of 0.5×10^9/L or greater over three consecutive days. The graft was considered to have failed in patients who survived more than 28 days after transplantation and did not achieve myeloid engraftment. Platelet engraftment was defined as the first day of a platelet count of 20×10^9/L or greater without needing transfusion support for at least 1 week. Mixed donor chimerism was defined as the presence of less than 90% of donor hematopoiesis.

Statistical analyses

χ^2 tests with Yates' correction were used to analyze differences in the distribution of categorical variables among subsets of patients. Mann–Whitney non-parametric U and Student's *t* tests were used to analyze differences in continuous variables. *p* values were calculated using two-tailed tests. Biological continuous variables were categorized using the median value. The probability of engraftment was estimated as the cumulative incidence. The competing risk for engraftment was death before day +28 without neutrophil or platelet recovery. The competing risks for transplant-related mortality were relapse and second transplant for patients with primary graft failure. Curves were compared by log–rank

testing. The optimal cut-off point for mixed donor chimerism to predict primary failure of engraftment was investigated using receiver operating characteristics (ROC) curves. The cut-off point was selected according to the best sensitivity and specificity detected in the curve. Computations were performed using the 11.0 version of SPSS software (SPSS Inc., Chicago, IL, USA).

Results

Characteristics of the patients

The characteristics of the patients and their transplants are summarized in Table 1. All 71 donor–recipient pairs displayed informative STR markers. Overall, 20 patients (28%) showed mixed hematopoietic chimerism at day 14 after CBT.

Kinetics of myeloid engraftment

The cumulative rate of myeloid engraftment among the recipients was 96% by day 60 (median time to myeloid recovery 20 days). Factors affecting the probability and the speed of myeloid engraftment are listed in Table 2. As shown in Figure 1, the chimerism status was related to the speed of myeloid recovery. The cumulative incidence of myeloid engraftment at 1 month after CBT was significantly lower for patients with mixed donor chimerism at day +14 (55% *vs.* 94%; $p<0.0001$). For patients achieving myeloid recovery, the median time of myeloid engraftment was 16 days when donor chimerism at day +14 was higher than 90%, compared with 24 days when donor chimerism was below this level ($p<0.001$). The cumulative incidence of engraftment was also significantly influenced by the CD34$^+$ cell dose infused ($p=0.0002$) and the number of colony-forming units infused ($p=0.02$). In a Cox regression model, only chimerism status at day +14 and the number of CD34$^+$ cells infused emerged as independent factors significantly influencing the probablility of myeloid

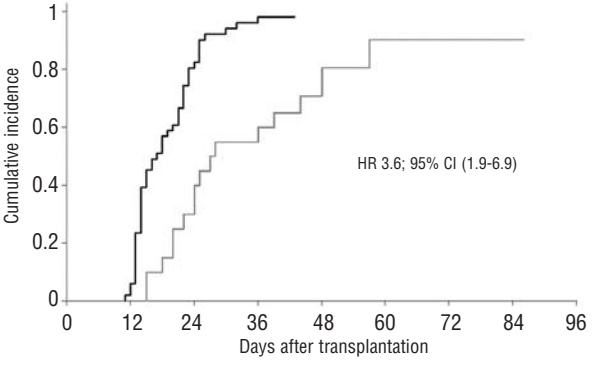

Figure 1. Cumulative incidence of myeloid engraftment according to donor chimerism status at day +14. The upper black line indicates the probability of myeloid recovery for patients with complete donor chimerism. The lower gray line indicates the probability of myeloid engraftment for patients with mixed donor chimerism ($p<0.0001$).

Table 1. Characteristics of the patients and their transplants.

Characteristics	Number of patients (%)
Median age (range in years)	32 (15-49)
Gender	
Male	47 (66)
Female	24 (34)
Diagnosis	
AML/MDS	28 (39)
ALL	27 (38)
CML	7 (10)
Others	9 (13)
Conditioning regimen	
BUCY-TT-ATG	42 (59)
BUFLU-TT-ATG	29 (41)
Donor–recipient HLA match	
6/6	7 (10)
5/6	22 (31)
4/6	52 (59)
Median weight (kg)	72 (44-112)
Median TNC infused[1] ($\times10^7$/kg)	2.25 (1.03-4.86)
Median CFU-GM infused[1] ($\times10^4$/kg)	2.59 (0.04-29.62)
Median CD34$^+$ infused cells[1] ($\times10^5$/kg)	1.18 (0.27-5.68)

[1]After thawing. AML: acute myeloid leukemia; MDS: myelodysplastic syndrome; ALL: acute lymphoblastic leukemia; CML: chronic myeloid leukemia; BUCY-TT-ATG: conditioning with busulfan, cyclophosphamide, thiotepa and antithymocyte globulin; BUFLU-TT-ATG: conditioning with busulfan, fludarabine, thiotepa and antithymocyte globulin; TNC: total nucleated cells; CFU-GM: colony-forming units of granulocyte macrophages.

Table 2. Factors influencing the cumulative incidence of myeloid engraftment.

	CI at 1 month	p univariate	p multivariate
Recipients' age			
< 32 years	0.80	0.9	
> 32 years	0.86		
Patient's gender			
male	0.79	0.2	
female	0.92		
HLA match			
matched	0.71	0.6	
mismatched	0.84		
Conditioning			
cyclophosphamide	0.81	0.2	
fludarabine	0.86		
Recipients' weight			
> 72 kg	0.81	0.5	
< 72 kg	0.86		
TNC$\times10^7$/kg			
> 2.25	0.86	0.02	
< 2.25	0.8		
CFU-GM$\times10^4$/kg			
> 2.59	0.94	0.02	
< 2.59	0.71		
CD34$^+$ cells$\times10^5$/kg			
> 1.4	0.94	0.0002	0.003
< 1.4	0.72		
Donor chimerism			
> 90%	0.94	<0.0001	<0.001
< 90%	0.55		

CI: cumulative incidence; TNC: total nucleated cells; CFU-GM: colony-forming units of granulocyte macrophages.

engraftment. The value of chimerism status at day +14 for predicting myeloid engraftment also remained significant in the subset of patients receiving the lower cell dose (p=0.0002).

Primary graft failure

Five patients did not achieve myeloid engraftment after a minimum of 43 days of follow-up. Three of them died, on days +47, +48 and +86. The remaining two underwent second transplants from HLA-mismatched family donors, both on day 43 after CBT, resulting in hematopoietic recovery.

Chimerism status at day +14 significantly influenced the incidence of primary graft failure. The best cut-off point for donor chimerism to predict primary graft failure was 65%, with a sensitivity of 97% and a specificity of 80%. The area under the ROC curve was 0.826 (95% confidence interval 0.553-1.099; p=0.016). Four out of six patients (67%) with less than 65% donor chimerism at day +14 suffered from primary graft failure as compared to only one of 65 patients (2%) with more than 65% donor chimerism (p<0.001). Additionally, as shown in Figure 2, the cumulative incidence of myeloid engraftment was 38% for the six patients with less than 65% donor chimerism compared with 95% for patients with more than 65% donor chimerism (p=0.0009).

No late bone marrow failure was observed in patients with mixed chimerism at day +14.

Platelet engraftment

The cumulative rate of platelet engraftment among the recipients was 82% by day 180 (median time to platelet recovery 51 days). Factors related to platelet engraftment are summarized in Table 3. As shown in Figure 3, the cumulative incidence of platelet engraftment at day +180 was higher for patients with full donor chimerism than for those with mixed chimerism (89% *vs.* 62%; p=0.01) and for those receiving more than 1.4×10^5/kg CD34$^+$ cells (92% *vs.* 72%; p=0.04). The value of chimerism status at day +14 for predicting platelet engraftment also remained in the subset of patients receiving the lower cell dose (p=0.02).

Graft-versus-host disease and transplant related mortality

Nineteen patients (27%) developed acute GVHD of more than grade 1. The incidence of acute GVHD of more than grade 1 was 30% for patients with mixed chimerism at day +14 as compared with 26% for those with complete donor chimerism (p=0.7). The cumula-

Table 3. Factors influencing the cumulative incidence of platelet engraftment.

	CI at 6 months	p univariate	p multivariate
Recipients' age			
<32 years	0.93	0.04	
>32 years	0.68		
Patient's gender			
male	0.78	0.3	
female	0.96		
HLA match			
matched	1	0.2	
mismatched	82		
Conditioning			
cyclophosphamide	0.83	0.3	
fludarabine	0.82		
Recipients' weight			
>72 kg	0.77	0.07	
<72 kg	0.85		
TNC			
$>2.25\times10^7$/kg	0.97	0.03	
$<2.25\times10^7$/kg	0.70		
CFU-GM			
$>2.59\times10^4$/kg	0.74	0.2	
$<2.59\times10^4$/kg	0.88		
CD34$^+$ cells			
$>1.4\times10^5$/kg	0.92	0.04	0.007
$<1.4\times10^5$/kg	0.72		
Donor chimerism			
>90%	0.89	0.01	0.02
<90%	0.62		

CI: cumulative incidence; TNC: total nucleated cells; CFU-GM: colony-forming units of granulocyte macrophages.

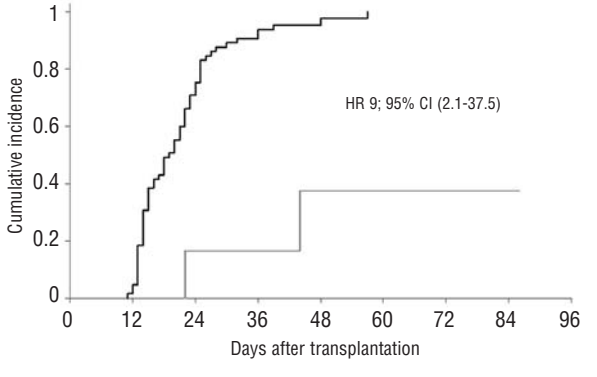

Figure 2. Cumulative incidence of myeloid engraftment according to donor chimerism status at day +14. The upper black line indicates the probability of myeloid recovery for patients with more than 65% donor chimerism. The lower gray line indicates the probability of myeloid engraftment for patients with less than 65% donor chimerism (p=0.0009).

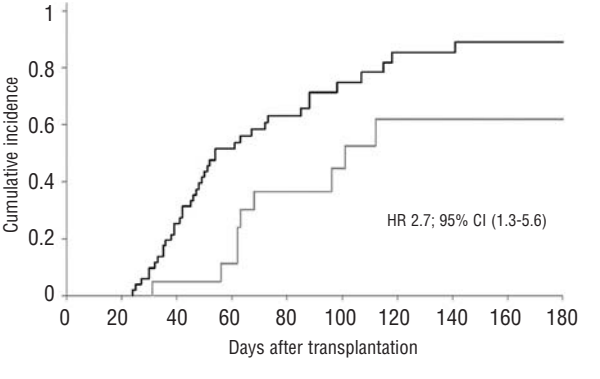

Figure 3. Cumulative incidence of platelet engraftment according to donor chimerism status at day +14. The upper black line indicates the cumulative incidence of platelet recovery for patients with more than 90% donor chimerism. The lower gray line indicates the cumulative incidence of platelet engraftment for patients with less than 90% donor chimerism (p=0.01).

tive incidence of transplant-related mortality 1 year after transplantation was 36% for patients with complete donor chimerism at day +14 and 50% for patients with mixed donor chimerism (p=0.4).

Discussion

We found that, in addition to CD34$^+$ cell dose at infusion, the hematopoietic chimerism status assessed at day +14 was an independent factor predicting myeloid engraftment after CBT in adults with hematologic malignancies. Chimerism status at day +14 has also been found to be associated with the kinetics of myeloid and platelet engraftment.

Studies of chimerism status as a predictive factor of engraftment after HSCT have mainly focused on graft loss after initial engraftment rather than on primary graft failure.[13,15-18,20-22] Information on the value of chimerism assessment to predict primary graft failure is scarce, and arises from studies performed in the setting of peripheral blood or bone marrow HSCT.[14,23] Those results showed that patients with mixed chimerism soon after HSCT had a higher incidence of primary graft failure.[14,23] This association would be especially important after CBT because of the characteristic susceptibility of this type of transplant to delayed engraftment and the high incidence of primary graft failure, and for instigating prompt therapeutic interventions.

Since primary graft failure is an early event after transplantation, the chimerism status in our study was assessed at a single time point at day +14. Although some reports using single-point analysis of chimerism were able to predict graft rejection,[18,20] longitudinal monitoring has been suggested to enhance the clinical value of chimerism assessment, mainly after HSCT without myeloablative conditioning.[22] Although more intensive monitoring could be useful for patients at high risk of primary graft failure or for monitoring therapeutic interventions, further studies on longitudinal testing are warranted to ascertain its role in predicting engraftment after CBT.

The extremely low cellularity in the peripheral blood at day +14 in the vast majority of patients led us to choose bone marrow to perform the chimerism analysis. In addition, in a situation of severe bone marrow hypoplasia, in which commonly low levels of DNA could be obtained, we consider that analysis of specific leukocyte subsets is at least technically challenging.[22] We, therefore, planned the study to be done in unmanipulated bone marrow.

The number of CD34$^+$ cells contained in the cord blood unit after thawing for infusion was confirmed as an important factor influencing myeloid and platelet engraftment. Several studies have demonstrated the impact of cell dose on engraftment in both adults and children.[7,24-27] However, the best indicator of cell dose remains controversial. Whereas total nucleated cell dose has been shown to be an important prognostic factor,[7,25,26] data from several reports suggest that the number of CD34$^+$ cells and colony-forming unit type granulocyte macrophages are better predictors of patients' outcomes.[27,28] Because the measurement of CD34$^+$ cells is not standardized, making it difficult to compare between different laboratories, its value as an indicator of cord blood quality at cryopreservation for cord blood unit selection is still unclear.[29] This single-center study with homogenous measurements of CD34$^+$ cells overcame this variability and highlights the impact of CD34$^+$ cell dose on engraftment. Efforts to standardize the technique so that CD34$^+$ counts can be used as a reliable measurement for cord blood unit selection are warranted.

The information provided by chimerism assessment 14 days after CBT could be clinically useful. Some studies suggest that the reduction or withdrawal of immunosuppression in the management of patients with mixed chimerism could improve the probability of engraftment.[21,30] In our study, patients with donor chimerism levels lower than 65% were shown to be at high risk of primary graft failure. In these cases and when autologous back-up is not available, planning of stem cell rescue using an alternative donor is advisable so that if engraftment finally does not occur, a rescue can be attempted without delay. In the present series, two patients were rescued using a haploidentical transplant resulting in rapid recovery from neutropenia.

In conclusion, hematopoietic chimerism status at day +14 correlated with the kinetics of myeloid and platelet engraftment and with the incidence of primary graft failure after single-unit CBT for adult patients with hematologic malignancies. This, together with a cell dose lower than 1.4×10^5/kg CD34$^+$ cells, provides very valuable information for predicting the outcome of the graft and could be clinically relevant for the management of adult patients undergoing CBT.

Authorship and Disclosures

F.M and JS conceived the study and analyzed and interpreted the data; FM, JM, GFS and MAS wrote the paper; FM performed the statistical analysis; LS and FM performed the studies on chimerism and collected the data; FM, JS, LS, SC, JR, PM, DP, IL, JC, JP and GFS included data on patients, managed patients, reviewed the manuscript and contributed to the final draft; MAS and GFS performed the final revision of the manuscript and approved the final draft.

The authors reported no potential conflicts of interest.

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