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Donor type, in Addition to Transplantation in Chronic Phase and Myeloablative Conditioning, Influence Transplant Survival for Patients with Advanced Chronic Myeloid Leukemia in the Era of Tyrosine Kinase Inhibitors

Piyanuch Kongtim[#1,4], **Kehinde Adekola**[#1], **Denái R. Milton**[2], **Reshma Ramlal**[1], **Antonio Jimenez**[1], **Julianne Chen**[1], **Gabriela Rondon**[1], **Sairah Ahmed**[1], **Partow Kebriaei**[1], **Oran Betul**[1], **Chitra M. Hosing**[1], **Uday Popat**[1], **Issa Khouri**[1], **Elias Jabbour**[3], **Jorge E. Cortes**[3], **Hagop M. Kantarjian**[3], **Richard E. Champlin**[1], and **Stefan O. Ciurea**[1]

[1]Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX

[2]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX

[3]Department of Leukemia The University of Texas MD Anderson Cancer Center, Houston, TX

[4]Division of Hematology Department of Medicine Faculty of Medicine Thammasat University, Thailand (current affiliation)

[#] These authors contributed equally to this work.

To the editor:

Treatment of patients with chronic myeloid leukemia (CML) has changed dramatically over the years with the introduction of tyrosine kinase inhibitors (TKIs), now considered standard upfront therapy for this disease. Despite promising results, outcome of patients who present in advanced-phase or who progress while on TKI therapy is poor.(l, 2) Allogeneic hematopoietic stem cell transplantation (AHSCT) remains the only potentially curative option for patients with advanced CML.(3)

Here we conducted a retrospective single-center study to assess the clinical benefit of AHSCT in patients with advanced-phase CML in the recent era of TKIs. We also evaluated transplant outcomes including the novel composite endpoint of graft-versus-host-free, relapse-free survival GRFS.(4) In addition, in light of recent improvements with haploidentical (HAPLO) donors, we assessed transplant outcomes by donor type.

AUTHORSHIP CONTRIBUTIONS

P.K. collected data and wrote the manuscript; K.A. collected data, reviewed and approved the manuscript; D.R.M analyzed data, interpreted the results, reviewed and approved the manuscript; R.R, A.J, J.C, G.R. contributed with data collection, reviewed and approved the manuscript; S.A., P.K., C.M.H., I.K., E.J., O.B., U.P., J.C., H.M.K., R.E.C. contributed with treatment of patients, reviewed and approved the manuscript; S.O.C. contributed with study design, data collection and interpretation, and manuscript writing.

CONFLICT OF INTEREST

The authors declare no competing financial interests to disclose for this work.

All consecutively treated patients with advanced CML, defined as beyond first chronic phase (CP1) who progressed to accelerated (AP) or blastic-phase (BP) treated from 01/2000-08/2015 at MD Anderson Cancer Center (MDACC) were included in this analysis. All patients provided written informed consent for transplant in accordance with the Declaration of Helsinki. The Institutional Review Board of MDACC approved the treatment protocols and this retrospective study.

Conditioning regimens varied; patients received either myeloablative (MAC) or reduced-intensity conditioning (RIC) according to CIBMTR criteria.(5) GVHD prophylaxis for HLA matched transplants consisted of tacrolimus and methotrexate of 5 mg/m^2 intravenously on day +1, +3, +6 and +11. Patients who received transplantation from HLA-matched unrelated or mismatched donors also received of anti-thymocyte globulin (15 mg/kg). GVHD prophylaxis regimen for HAPLO transplantation was with cyclophosphamide 50 mg/kg/day on day +3, +4 (PTCy), tacrolimus and mycophenolate mofetil.

Hematologic, cytogenetic, and molecular responses pre- and post-transplant were defined according to the European LeukemiaNet response criteria.(6) The primary endpoint was progression-free survival (PFS). Secondary endpoints included GVHD-free, relapse-free survival (GRFS; defined as the first event among aGVHD grades III-IV, extensive cGVHD, molecular relapse, and death)(4), overall survival (OS), treatment-related mortality (TRM), relapse, acute GVHD (aGVHD) and chronic GVHD (cGVHD). Molecular relapse was defined as previously described.(7) The Kaplan-Meier method was used to estimate all survival measures. Differences in survival between groups were assessed using the log-rank test. Associations between post-transplant outcomes and patient subgroups of interest were determined using univariate Cox proportional hazards regression models (UVA). A multivariable Cox proportional hazards regression model (MVA) was used to determine the association between the post-transplant outcomes and those measures with p-values <0.10 in the univariate assessments. The cumulative incidence (CI) function with the competing risks method was used to estimate the endpoints of relapse, TRM, aGVHD, and cGVHD. Differences in CI between donor types were assessed using Gray's test. All statistical tests used a significance level of 5%.

Patient demographics and transplant characteristics are listed in Table 1. Two hundred and seven consecutive advanced CML patients with median age of 44 years were evaluated in this study. Disease status at the time of transplant according to WHO criteria(8) was CP2, AP and BP in 160 (77%), 24 (12%) and 14 (7%) patients, respectively, and 9 (4%) patients had missing data. Donors were matched related (MRD), matched unrelated (MUD), HAPLO, mismatched unrelated (MMUD), umbilical cord blood (UCB) and 1 antigen mismatched related (MMRD) in 79 (38%), 75 (36%), 18 (9%), 17 (8%), 11 (5%) and 7 (3%) patients, respectively. There was no significant difference in demographic data of the patients in each donor type. The median time from diagnosis to transplant was 27 months (range 1.5-318 months). The median follow-up duration of patients who survived at last follow-up was 60 months.

The CI of aGVHD grades II-IV at 1 year post-transplant was 35%, whereas the CI of extensive cGVHD at 5 years was 31%. The CI of TRM at 1 year was 24%. There was no

significant difference in the CI of severe aGVHD or cGVHD between donor types. The CI of cytogenetic and molecular relapse at 5 years post-transplant was 22% and 31%, respectively. For the entire group, the probability of PFS, OS and GRFS at 5 years was 49% and 22%, respectively. The median OS for patient in CP2, AP and BP were 97, 8 and 7 months, respectively.

Adjusting for all significant factors, transplantation in CP2, using a HAPLO donor and MAC regimen were significantly associated with better PFS in MVA. The 5-year PFS of patients in CP2, AP and BP was 38%, 23% and 14%, respectively (p=0.007) (Figure 1A). The 5-year PFS according to donor type was 59%, 36%, 34%, 29%, 14% and 18% in HAPLO, MRD, MUD, MMUD, MMRD, and UCB group, respectively (p=0.080). Patients receiving a HAPLO donor had better 5-year PFS when compared with HLA matched related and unrelated donor transplants, though not statistically significant (59% vs. 35%, p=0.11) (Figure 1B).

For GRFS, transplant in CP2 and using HAPLO donor were significantly associated with better GRFS in MVA. The 5-year GRFS of patients in CP2, AP and BP before transplant was 24%, 16% and 14%, respectively (p=0.013) (Figure 1C). The 5-year GRFS according to donor type was 53%, 19%, 23%, 29%, 0% and 9% in HAPLO, MRD, MUD, MMUD, MMRD and UCB group, respectively (p=0.060). Patients receiving a HAPLO donor had a better 5-year GRFS when compared with HLA matched related and unrelated donor transplants (53% vs. 21%, p=0.019) (Figure 1D).

AHSCT remains a standard approach for patients with advanced CML.(3, 9) The largest retrospective study from the Center for International Blood and Marrow Transplant Research (CIBMTR) showed a 3-year PFS of 37%, 27% and 10% for patients in AP, CP2 and BP respectively.(3) Our results show a similar 5-year PFS for patients with advanced CML of 34% with a CI of cytogenetic and molecular relapse at 5 years of 22% and 31%, respectively.

In order to better appreciate the success of transplantation, we also analyzed a novel composite endpoint, GRFS, which reflects not only disease-free survival but also takes into consideration two major transplant complications, severe acute and chronic GVHD. Using this endpoint, 22% of patients survived to 5 years without experiencing a GRFS-defining event. This demonstrates that a large proportion of transplant survivors will be affected by significant GVHD-related complications. The use of post-transplantation cyclophosphamide (PTCy), which has been shown to be associated with significantly lower incidence of severe acute and chronic GVHD in HAPLO transplants(10, 11) may impact GRFS for HLA matched transplants also; however, this remains to be determined.

The prognostic significance of disease phase pre-transplant has previously been established in several studies.(1, 9, 12) Transplantation in AP or BP has been shown to be associated with significantly worse outcomes, including by our group.(9, 12) Our study clearly showed that patients who returned to CP2 from AP or BP were more likely to achieve a post-transplant CCgR, and more than MMoIR, which translated into a better survival when compared with patients transplanted in AP or BP.

In the absence of an HLA matched donor, a HAPLO donor is the most accessible stem cell source as most patients will have a haplotype matched related donor in their immediate family. Due to effective GVHD prophylaxis using PTCy, outcomes of allografting with HAPLO donors have improved significantly with multiple retrospective studies now showing similar outcomes between HAPLO and HLA matched transplants.(10, 11, 13–15) However, no study reported outcomes of patients treated with PTCy for patients with CML. We found that HAPLO transplantation performed with PTCy-based GVHD prophylaxis was associated with very low incidence of severe acute and chronic GVHD and better GRFS compared with other donor types. This might reflect not only the effectiveness of PTCy to control severe GVHD in this setting, but also a stronger GVT effect, since CML is one of the most sensitive hematological malignancies to a GVT effect. Although patients were not randomly selected into different donor groups and we had limited numbers of patients in each group, these results suggest that HAPLO transplantation with PTCy may be at least as effective as HLA-matched donor transplants performed with conventional GVHD prophylaxis for patients with advanced CML. Using a HAPLO donor could be considered if there is urgent need to proceed to transplant and a MUD is not immediately available. A prospective study with a sufficiently large number of HAPLO transplantations is needed to confirm the validity of the data.

In conclusion, our results indicate that, in addition to MAC and transplantation in CP2, AHSCT using HAPLO donors offers at least as good PFS and GRFS as HLA matched transplants using conventional GVHD prophylaxis. Future studies will determine if this is largely a PTCy-based GVHD prophylaxis effect or outcomes are indeed improved with HAPLO transplants also because of a stronger GVT effect, which is known to occur in patients with CML.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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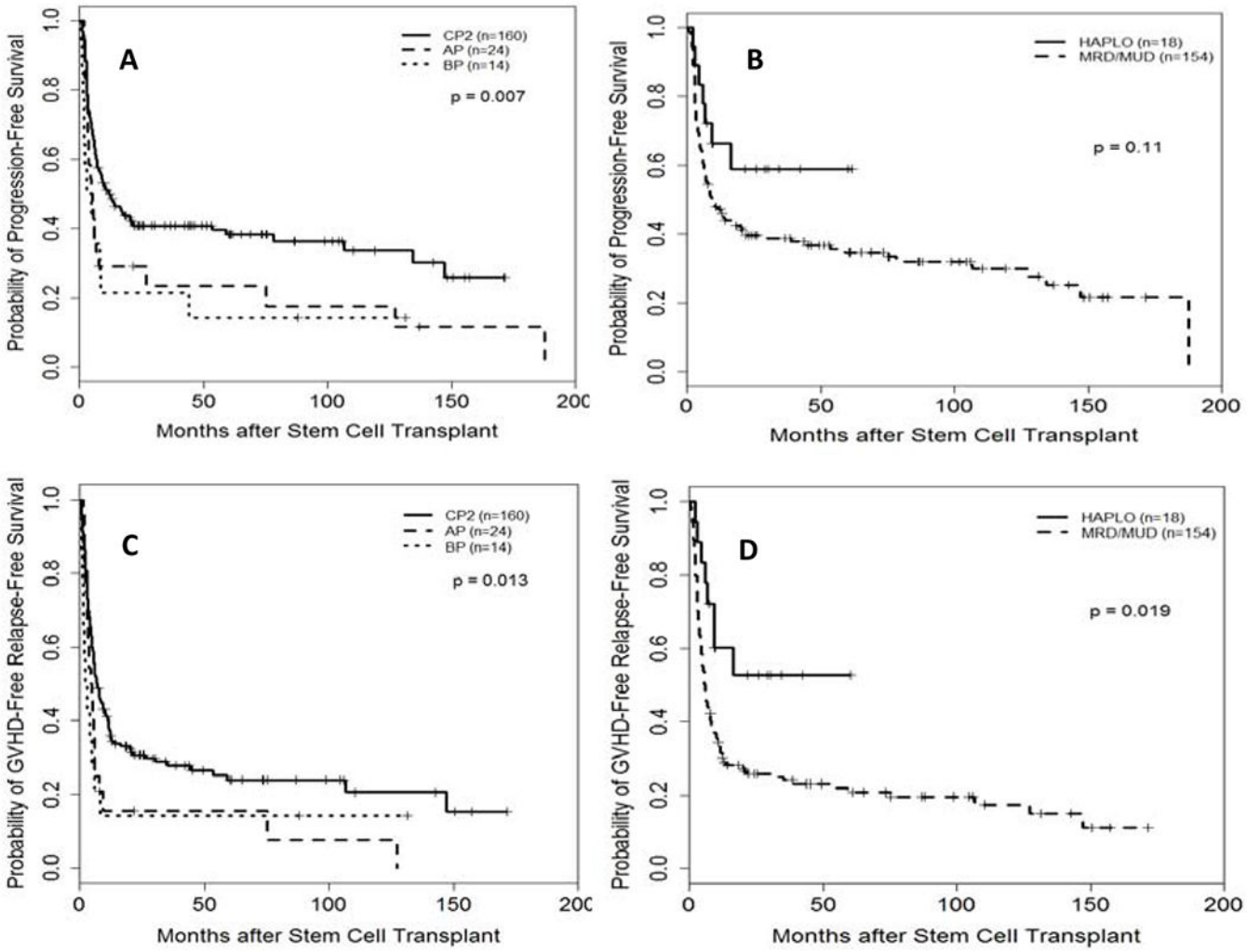

Figure 1.

PFS by disease phase at transplant (A); PFS by donor type (B); GRFS by disease phase at transplant (C) and GRFS by donor type (D)

Table 1.

Patient and transplant characteristics

Characteristics	All Patients (N=207)
Gender, n (%)	
Male	135 (65)
Female	72 (35)
Median age (years)	44 (range 2 – 70)
Ethnicity, n (%)	
White	140 (68)
Hispanic	30 (15)
Black	28 (14)
Other	7 (3)
Missing	2
Disease phase at transplant	
≥ CP2	160 (77)
AP	24 (12)
BP	14 (7)
Missing	9 (4)
Cytogenetic response prior to transplant, n (%)	
≥CCgR	71 (34)
Less than CCgR	129 (63)
Missing	7 (3)
Clonal cytogenetic evolution, n (%)	31 (15)
Molecular response prior to transplant, n (%)	
≥MMolR	12 (6)
<MMolR	176 (85)
Missing	19 (9)
***BCR-ABL* KD mutation analysis, n=114 (%)**	
Negative	67 (59)
Positive	40 (35)
Indeterminate	7 (6)
T315I kinase domain mutation, n=114 (%)	10 (9)
Donor type, n (%)	
MRD	79 (38)
MUD	75 (36)
HAPLO	18 (9)
MMUD	17 (8)

Characteristics	All Patients (N=207)
UCB	11 (5)
MMRD	7 (3)
Donor mismatch, n (%)	
Female-to-male	57 (28)
Other	148 (72)
Missing	2
Blood type donor/recipient mismatch, n (%)	
Major	60 (30)
Minor	30 (15)
Match	113 (56)
Missing	4
Conditioning regimen intensity, n (%)	
MAC	140 (68)
RIC	67 (32)
Time from diagnosis to transplant (months), median (range)	27 (1.5 – 318)
Follow-up duration of survivors (months), median (range)	60 (7.3 – 194)

Abbreviations: CP2: second chronic phase; AP: accelerated phase; BP: blastic phase; TKIs: tyrosine kinase inhibitors; ASCT: autologous stem cell transplantation; CCgR: complete cytogenetic response; MMolR: major molecular response; MRD: matched related donor; MUD: matched unrelated donor; HAPLO: haploidentical donor; MMUD: mismatched unrelated donor; UCB: umbilical cord blood donor; MMRD mismatched related donor; MAC myeloablative conditioning; RIC: reduced intensity conditioning