Validation of the EBMT risk score in chronic myeloid leukemia in Brazil and allogeneic transplant outcome

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Background and Objectives. The management of chronic myeloid leukemia (CML) has changed radically since the introduction of imatinib therapy. The decision of whether to offer a patient a hematopoietic stem cell transplant (HSCT) must be based on the probability of success of the procedure. The aim of this retrospective analysis of 1,084 CML patients who received an allogeneic HSCT in 10 Brazilian Centers between February 1983 and March 2003 was to validate the EBMT risk score.

Design and Methods. The study population comprised 647 (60%) males and 437 (40%) females, with a median age of 32 years old (range 1 - 59); 898 (83%) were in chronic phase, 146 (13%) were in accelerated phase and 40 (4%) were in blast crisis; 151 (14%) were younger than 20 years old, 620 (57%) were between 20 and 40 and 313 (29%) were older than 40; 1,025 (94%) received an HLA fully matched sibling transplant and only 59 (6%) received an unrelated transplant. In 283 cases (26%) a male recipient received a graft from a female donor. The interval from diagnosis to transplantation was less than 12 months in 223 (21%) cases and greater in 861 (79%). The overall survival, disease-free survival, transplant-related mortality and relapse incidence were 49%, 50%, 45% and 25%, respectively.

Results. Of the 1084 patients, 179 (17%) had a risk score of 0 or 1, 397 (37%) had a score of 2, 345 (32%) had a score of 3, 135 (12%) had a score of 4 and 28 (2%) a score of 5 or 6. The overall survival (OS) rate in patients with risk scores 0-1 and 2 was similar (58% and 55%, respectively) but significantly better than that in patients with scores 3 or more (score 3 - 44%, 4 - 36 % and 5-6 - 27%, respectively) (p<0.001). Disease-free survival (DFS) and transplant related mortality (TRM) in a patients with a score of 3 or more were 46% and 49%, respectively and the relapse rate beyond score 5-6 was 77%. Disease status had a negative impact on all outcomes (OS, DFS, TRM, and relapse). The OS rate for male recipients of a graft from a female donor was 40% compared to 52% among the other donor-recipient pairs (p=0.004). DFS and TRM were significant for disease phase and female donor-male recipient (p<0.001 and p<0.003, respectively). In our experience, age and interval between diagnosis and transplant did influence OS, DFS, TRM, and relapse rate.

Interpretation and Conclusions. Our results validate the EBMT risk score in the context of a developing country and confirm its usefulness for making point decisions in the imatinib era.

Key words: allogeneic hematopoietic stem cell transplantation (HSCT), chronic myeloid leukemia, EBMT risk scores.

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The approach to primary treatment for patients with newly diagnosed chronic myeloid leukemia (CML) has changed as a result of the effectiveness and safety of imatinib mesylate.[1-6] This drug has shown activity in all phases of CML but the best responses are seen in the early chronic phase.[7-11] The results of the IRIS study of imatinib alone versus interferon-α (IFN-α) plus cytarabine (Ara-C) showed that the chance of preventing progression to accelerated phase or blast crisis was 97% in a median time of 18 months for patients receiving imatinib alone versus 93% for those who received IFN-α plus Ara-C. This was accompanied by a significant increase in the number of patients achieving a major cytogenetic response (MCR) or a complete cytogenetic response (CCR) to 87% and 76%, respectively for patients receiving imatinib versus 34% and 15% for those treated with IFN-α plus Ara-C.[11] However, 20-30% of newly diagnosed patients receiving 400 mg/day of imatinib fail to achieve a good molecular response[11] and a small proportion has undetectable levels of *BCR-ABL* transcripts.[12] *BCR-ABL* positive hematopoietic progenitors persist in the marrow of patients in CCR, indicating that

the malignant progenitor may be suppressed but not eliminated during imatinib treatment.[13] Besides these considerations, concerns exist regarding the development of resistance to imatinib.[14–18]

Allogeneic hematopoietic stem cell transplantation (HSCT) results in long-term disease control and may cure selected patients with CML, depending on the contribution of the graft-versus-leukemia effect.[19–21] Comparisons of survival rates afforded by various treatments are used to formulate general treatment policies but the decision on whether or not to offer an allogeneic HSCT should be based on the probability of success using this procedure. Prognostic scores incorporating patient – and disease–specific variables can assist this decision-making.[22] The European Blood and Marrow Transplant Group (EBMT) devised a prognostic score for patients receiving allogeneic HSCT based on five variables: donor type, stage of disease, recipient age, donor-recipient sex match and interval from diagnosis to transplant. The different scores resulted in substantially different survival rates[23] and this risk score was recently validated by the International Bone Marrow Transplant Registry.[22] In the imatinib era and in situations with limited resources we need information regarding the best chance to benefit from HSCT. Our aim was to validate the EBMT risk score in a Brazilian population in order to be able to give adequate counseling and take decisions in the imatinib era.

Table 1. Distribution of patients according to gender and variables of the EBMT risk score.

Status	*No. (%)*
chronic phase	898 (83)
accelerated phase	146 (13)
blast crisis	40 (4)
Age (years)	
< 20	151 (14)
20-40	620 (57)
>40	313 (29)
Gender of patient	
male	647 (60)
female	437 (40)
HLA - full match	
identical sibling	1,025 (94)
unrelated	59 (6)
Gender match donor/recipient	
female/male	283 (26)
other	801 (74)
Time from diagnosis	
<12 months	223 (21)
>12 months	861 (79)

Design and Methods

This retrospective study is based on data from 1,084 patients who underwent an allogeneic HSCT for CML from an HLA-identical sibling or unrelated donor in 10 Brazilian centers between February 1983 and March 2003. The EBMT score was not used as an eligibility criterion for transplant all the time. No patients had previously received imatinib. A standardized questionnaire was provided to each institution to collect the data, which included details of the patient's age and sex, donor sex, stage of disease, histocompatibility, time from diagnosis to transplant and outcome. The stage of disease was classified according to International Bone Marrow Transplant Registry.[24] Overall survival and transplant-related mortality were also recorded for different periods of time.

EBMT risk-score

The variables were defined as those used to calculate the original EBMT risk score and categorized as reported by Gratwohl *et al.*,:[23] age (under 20, between 20-40, over 40 years old); interval from diagnosis to transplant, (>1 and ≤1year); disease status (chronic, accelerated or blast crisis); donor-recipient sex match (female donor for male patient versus other); and donor type (HLA-identical sibling versus unrelated donor). The risk-score for an individual patient is simply the sum of the scores for the risk factors used to calculate the published EBMT risk score:[23] donor type (0 for HLA-identical sibling donor, 1 for a matched unrelated donor); disease stage (0 for first chronic phase, 1 for accelerated phase, 2 for blast crisis or higher chronic phase); age of recipient (0 for < 20 years, 1 for 20 – 40 years, and 2 for > 40 years); sex match (0 for all, except 1 for male recipient /female donor); and time from diagnosis to transplantation (0 for < 12 months and 1 for > 12 months). No additional prognostic factor was included.

Statistical analysis

The statistical analysis was performed based on data of March 1st, 2003. The overall survival (OS), disease-free survival (DFS), transplant-related mortality (TRM) and relapse incidence (RI) were estimated using the Kaplan-Meier method and cumulative incidence whenever appropriate. Cumulative incidence was estimated using deaths unrelated to these causes as competing risks. The EBMT risk score was ana-

Table 2. Distribution of patients stratified according to EBMT score.

Score	N.	%
0-1	179	17
2	397	37
3	345	32
4	135	12
5-6	28	2

lyzed in a multivariate Cox proportional-hazards regression model. S-Plus software version 2000 was used.

Results

The characteristics of the patients according to the variables used to calculate the risk score are shown in Table 1. Eight hundred and ninety-eight patients (83%) were in first chronic phase, 620 (57%) were between 20 and 40 years old, 1,025 (94%) received grafts from HLA identical siblings, and the interval from diagnosis to transplant was greater than 12 months in 861 (79%) patients. In 283 (26%) cases a male recipient had a female donor. Only 59 patients (6%) received grafts from fullly matched unrelated donors. After a median observation time of 15 months (range: 1-213), the OS, DFS, TRM and RI were 49%, 50%, 45%, and 25%, respectively. Although not incorporated in the EBMT score, it is important to add that the source of stem cells was bone marrow in 1,040 cases (95.9%), peripheral blood progenitor cells in 40 (3.7%) and cord blood in just 4 (0.4%). The conditioning regimen used in 86% of the patients was busulfan (Bu) plus cyclophosphamide (CY), whereas 14% received a variety of other regimens (TBI + CY; Bu + melphalan; TBI + fludarabine; fludarabine + melphalan). Graft-versus-host disease (GVHD) prophylaxis in 94% of the patients was methotrexate plus cyclosporin A. The OS rate varied according to the different periods, being 56% for the years 1998-2003; 49% for 1993-1997; 38% for 1988-1992 and 25% for 1983-1987, showing a significant difference between the periods (p=0.001). TRM was also significantly different (p<0.001) between the periods being 39% for 1998-2003; 45% for 1993-1997; 59% for 1988-1992 and 75% for 1983-1987.

Table 2 shows the distribution of patients stratified according to EBMT risk score from 0 to 6. No patients had a score of 7. One hundred and seventy-nine patients (17%) had a score of 0 or 1, 397 (37%) had a score of 2, 345 (32%) had a score of 3, 135 (12%) had a score of 4, and the remaining 28 patients had a score of 5 or 6 (2%). The influence of risk score on outcome of the 1,084 patients is presented in Figure 1. Patients with a risk score of 3 or above had higher TRM and lower OS and DFS. The relapse rate was influenced by risk scores 5 and 6. In addition, disease phase had a negative impact on all outcomes (OS, DFS, TRM, and relapse) (Figure 2). The OS in chronic phase, in accelerated phase and in blast crisis was 55%, 28% and 14%, respectively (p<0.001). Furthermore, OS for male recipients transplanted from a female donor was 40% compared to 52% (p= 0.004). The patient's age and time from diagnosis to transplantation had no influence on the outcome.

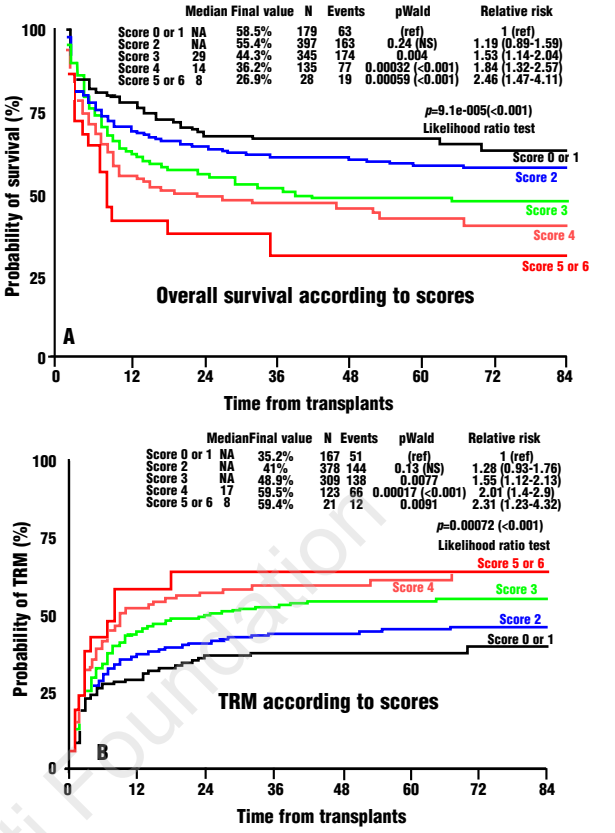

Figure 1. Overall survival according to EBMT risk scores (A) and transplant-related mortality (B).

Discussion

A large amount of data has been published in recent years regarding the use of imatinib as front-line therapy for CML. The high levels of hematolog-

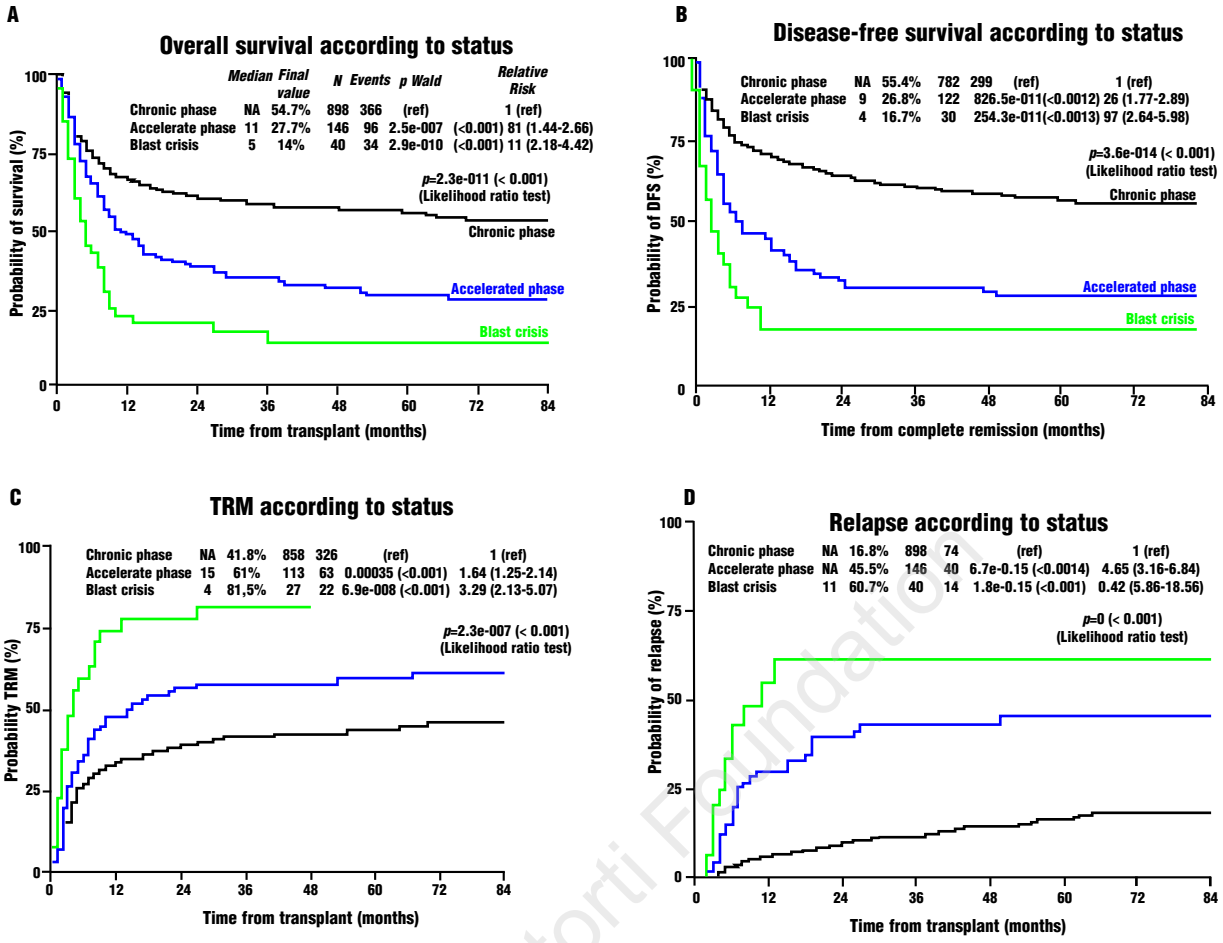

Figure 2. Overall survival (A), disease-free survival (B), transplant-related mortality (C) and relapse incidence (D) according to disease status.

ic and cytogenetic responses, combined with the drug's safety, have created a new and important paradigm in the treatment of CML. However, low levels of molecular response (about 5% using the conventional 400 mg/day dose[12] up to about 30% using a high dose of 800 mg/day,[25] primary and acquired resistance, and the possibility of progression, are the most important concerns that must be analyzed in order to be able to choose the most effective and least toxic approach. Allogeneic HSCT has been demonstrated to be able to cure CML in all clinical phases. However, the risks of high morbidity and TRM associated with acute and chronic GVHD must be considered against the benefit of HSCT. The present challenge is to identify subsets of patients best suited to receive either imatinib or HSCT. Based on our observation and important papers published by Gratwohl[23] and then by Passweg,[22] patients with low EBMT risk scores (0 to 2) may be the subgroup best treated with HSCT. In fact, patients with a risk score of 3 or above who are treated with HSCT have a low OS and DFS and high TRM and relapse rate. In addition, the status of disease at transplantation is a powerful predictor of outcome. Patients in accelerated phase or in blast crisis have a very bad prognosis. Although HSCT might be the only treatment able to cure patients in advanced phase, only a few patients in this subgroup achieve a long and stable remission or definitive cure. There are currently two important points that need to be examined: (i) the increase in risk if imatinib is given first and transplants are performed only at progression or if imatinib fails; (ii) a definition of a cohort of patients with such a low chance of success with HSCT that it is not justifiable to use the limited resources.

This study was intended to present the results of CML patients treated with HSCT in a developing country and validate the EBMT risk score in the same context. The patients in the study represent

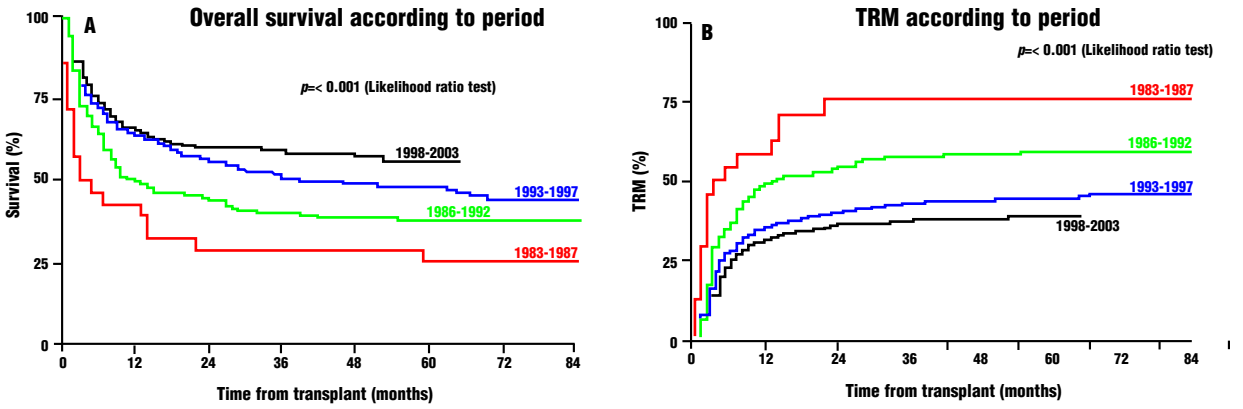

Figure 3. Overall survival (A) and TRM (B) according to period of time.

the evolution and history of 20 years of HSCT for CML in Brazil. Our data, in an independent population, demonstrate that the EBMT risk score is reliable and represents a useful guide for clinical decision-making. Our data differ slightly from those in Gratwohl's original study.[23] Advanced disease status and transplantation from a female donor into a male recipient were the factors with the worst prognostic impact, whereas patients' age and time from diagnosis to transplant were not significant in either univariate or multivariate analysis. These differences may be related to differences in the characteristics of the patients in the two populations: there were fewer patients in blast crisis in our study than in the original study (4% vs. 14%), our patients were much younger, as assessed by the proportion of patients younger than 20 years (14% in our study vs. 8% in the original study), and the time from diagnosis to transplantation was much longer (79% of our patients were transplanted >12 months after diagnosis, compared to 51% in the study by Gratwohl *et al.*). Regarding the time from diagnosis to transplant, we speculate that in our country there is a delay in making the diagnosis and referring the patient to a bone marrow transplant center. This has been reported to be the case for Brazilian patients with acute myeloid leukemia.[26]

OS and TRM showed a progressive improvement over time which could be predicted from the improvements in support treatment, modern typing, GVHD and CMV control. Despite these slight differences, our study validates the EBMT risk score[23] and confirms its usefulness for point-decision, especially in choosing the best treatment in the imatinib era.

CADS, ACV, MAR, MN and, RP were the principal authors. They were primarily responsible for this paper from the conception to the submission of the manuscript. The remaining authors qualified for authorship of the paper according to the World Association of Medical Editors (WAME) and take specific responsibility for the following parts of its content: FJPA, FLD, LS, AM and, AG revised it critically for important intellectual content. VMF, DT, AMA, RB, MCMM, RS, GBO, WMW, JCV, BPS, VC, FML, HB, MPDS and LR collected, analyzed and interpreted the data. RZ and ECMM were responsible for the statistical analyses. All the authors discussed and agreed on the final version of the paper. CADS was responsible for all Tables and Figures. The authors declare that they have no potential conflicts of interest.

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