

## Quality of life in patients randomized to receive a bone marrow or a peripheral blood allograft

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**Background and Objectives.** Quality of life (QOL) is an important clinical end-point to be considered in the late follow-up of patients treated with allogeneic bone marrow (BM) or peripheral blood progenitor cell (PBPC) transplantation.

**Design and Methods.** To assess the QOL in a group of survivors of hematologic malignancies who had been enrolled in a prospective randomized trial comparing allogeneic BM with PBPC. Sixty randomized patients had been enrolled in a study comparing BM with PBPC graft during 1995-99. At the time of this QOL study, 30 were alive and 26 (13 BM and 13 PBPC) were eligible. Clinical and demographic data were collected and psychometric instruments (WHOQOL-100 and the Hospital Anxiety and Depression Scale - HAD) were used. Non-parametric and univariate analyses were performed.

**Results.** The PBPC recipients had more chronic graft-versus-host disease ( $p=0.03$ ) and were on immunosuppressive treatment for a longer period ( $p=0.02$ ). The WHOQOL-100 analysis demonstrated significant differences between groups with more favorable results in the BM group in the facets of Pain and Discomfort ( $p=0.03$ ), Mobility ( $p=0.02$ ) and Daily Living Activities ( $p=0.03$ ). According to the patients' spontaneous responses, 8 individuals (6 in the PBPC group) believed that their QOL had worsened.

**Interpretation and Conclusions.** With the limitations of a small randomized study, these findings suggest a lower QOL in recipients of allogeneic PBPC than in recipients of BM grafts, probably due to the frequency and severity of chronic graft-versus-host disease. This need to be confirmed in a large international trial.

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Key words: allogeneic bone marrow transplantation; peripheral blood progenitor cell; quality of life; chronic GVHD; immunosuppression.

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## Stem Cell Transplantation



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Quality of life (QOL) is considered one of the most important clinical end-points related to long-term follow-up of allogeneic hematopoietic stem cell transplantation. Many papers concerning QOL in an increasing number of long-term survivors have been published.<sup>1-4</sup>

QOL depends on many factors including physical, occupational, cultural, social and psychological ones. Chiodi *et al.*<sup>5</sup> showed that about one third of 244 transplanted patients reported poor QOL after their transplant, associated mainly with old age, presence of long-term sequelae, chronic graft-versus-host disease (GVHD), short follow-up after transplant and gender. Data from Yano *et al.*<sup>6</sup> revealed that length of time since transplantation and the diagnosis of chronic GVHD were associated with worse QOL. Many randomized trials, and a retrospective registry analysis, have not yet clarified the role of PBPC as a source for an allogeneic hematopoietic stem cell transplantation. Many authors agree that PBPC transplant promotes a good and stable engraftment showing advantages in terms of neutrophil and platelet recovery, and lower transplant-related mortality, for patients with advanced-stage leukemia.<sup>7-14</sup> However, some studies have shown a significantly higher probability of chronic GVHD after allogeneic PBPC than after allogeneic bone marrow grafting.<sup>7,8,11,14</sup> In addition, significant differences in overall survival and disease-free survival have been found in favor of PBPC, largely because of lower transplant-related mortality in patients with advanced-stage disease.<sup>12-14</sup> The issue related to the best source of hematopoietic stem cell has not been yet clarified. Moreover, the correlation between QOL and chronic GVHD is one of the most important points to be identified in this field. As far as we know, there is no controlled QOL study comparing BM and PBPC as the source of graft for allogeneic transplantation. This study assesses the QOL in a group of survivors of hematologic malignancies who had been enrolled in a prospective randomized trial comparing allogeneic BM with PBPC.

## Design and Methods

### Patients

The study population consisted of all survivors who had participated in a prospective randomized study, comparing PBPC and BM transplantation, performed at the Bone Marrow Transplantation Unit, State University of Campinas, Brazil.<sup>7,15</sup> Thirty patients were alive on July 2000 and 26 of them met criteria for inclusion in the present study: age >16 years, follow-up >1 year, hematologic malignancy as primary disease and HLA-identical sibling donor. Four patients were not eligible (three were <16 years old and one had undergone a second transplant). Altogether 26 patients (13 PBPC and 13 BM recipients) participated in the study, all of them in complete remission (CR) (Figure 1) (Table 1).

### Instruments

Clinical and social demographic data were collected from the patients' medical records: age, marital status, primary disease, type of transplant, acute and chronic GVHD, duration of immunosuppressive treatment, present health and treatment.

*World Health Organization Quality of Life Instrument* (WHOQOL-100). This 100-item core of a generic QOL tool comprises 6 domains (physical, psychological, level of independence, social relationships, environment, spirituality/religion/beliefs) each of which covers several facets. Items are assessed on 5-point Likert scales, which are completed by the patients on their own. There are 25 facets. Each facet is calculated by summing the scores on the four items within each facet. All facet scores range from 4 to 20, with higher scores denoting higher quality of life, except for the facets Pain and Discomfort, Negative Feelings, and Treatment Dependence.<sup>16</sup>

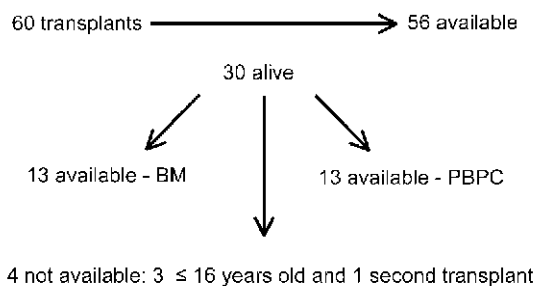
The WHOQOL-100 has been considered a reliable and valid instrument that can be used in a diverse range of cultural settings. Its Cronbach alphas demonstrate good internal consistency for the facets, ranging from 0.65 to 0.93 (*The WHOQOL Group, 1998*). The WHOQOL was previously validated in Brazil.<sup>17</sup> At completion of the WHOQOL, respondents were asked to assess if their quality of life, based on their experience over the last two weeks, was better, worse or had not changed since the month prior to the transplant.<sup>18,19</sup>

*Hospital Anxiety and Depression Scale (HAD)*. The HAD is a self-report instrument to identify and quantify symptoms of anxiety (7 multiple choice questions) and depression (7 questions). This instrument was designed for use in non-psychi-

**Table 1. Demographic and clinical characteristics.**

	PBPC (n=13)	BM (n=13)	p
Sex			
Female	6	6	
Male	7	7	NS
Age (years)			
Median	34	36	NS
Range	20-53	19-61	
Marital status			
Married	8	9	
Single	4	4	
Divorced	1	0	
Diagnoses			
CML - CR	10	11	
AML - CR	2	1	
MDS - CR	1	0	
ALL - CR	0	1	
Follow-up (days)			
Median	1123	1372	NS
Range	451-1977	444-1942	
Acute GVHD (grades II-IV)	2	2	
Chronic GVHD			
Localized	0	4	
Extensive	10	5	0.03*
Immunosuppressive treatment (days)			
Median	575	270	
Range	60-1530	270-360	0.02°

\*Fisher's test; °Wilcoxon's rank sum test, CML: chronic myeloid leukemia; AML: acute myeloid leukemia; MDS: myelodysplastic syndrome; ALL: acute lymphoblastic leukemia; CR: complete remission; Acute GVHD: acute graft-versus-host disease; chronic GVHD: chronic graft-versus-host disease.



**Figure 1. Flow chart of randomized patients treated with BM or PBPC.**

atric settings thus avoiding physical indicators of psychological distress, such as headache or weight loss, which could in fact be due to an underlying medical illness.<sup>20</sup> The global score for each scale

**Table 2. Scores on the WHOQOL domains and facets.**

	PBPC (n= 13)	BM (n= 13)	P°
Physical	13.3	16.0	0.08
Pain and discomfort*	14.0	11.0	0.03
Energy and fatigue	13.0	17.0	NS
Sleep and rest	16.0	19.0	NS
Psychological	14.8	15.6	NS
Level of independence	15.0	17.7	0.04
Mobility	16.0	18.0	0.02
Daily life activities	13.0	18.0	0.03
Treatment dependence*	10.0	6.0	NS
Work capacity	16.0	16.0	NS
Social relationships	15.0	16.6	NS
Sexual activity	14.0	17.0	0.09
Environment	13.1	14.2	NS
Health and social care	14.0	16.0	0.07
Spirituality/religion/beliefs	16.0	16.0	NS

\*These facets are scored in a negative direction (i.e. higher scores = lower quality of life). For the other facets, higher scores denote higher quality of life.

°Wilcoxon's rank sum test. NS = no statistical significance.

ranges from 0-21. The HAD was validated in Brazil and a cut-off of 8/9 for both anxiety and depression was used in this study.<sup>21</sup>

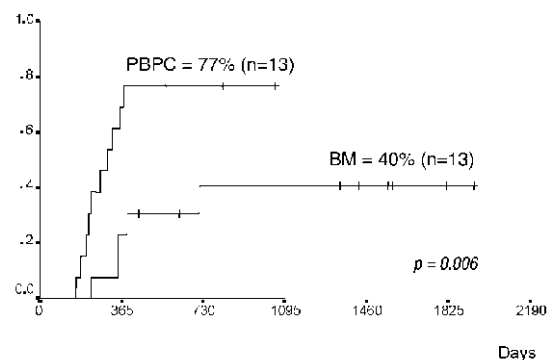
### Statistical Analysis

Continuous variables were compared with the Wilcoxon's and the Kruskal-Wallis' tests considering all  $p$  values < 0.05 as statistically significant. Proportions of patients within each group (PBPC or BM) were compared by the Fisher's test. The probability of chronic GVHD was analyzed using Kaplan-Meier product limit estimates<sup>22</sup> and Breslow's test.<sup>23</sup> Univariate and multivariate analyses were performed using a linear regression model. Facets and dominions were considered responses variables. Graft source (PBPC or BM), sex and extensive, chronic GVHD were considered explanatory variables. The statistical software packages used were the S-Plus 2000 and the SPSS 7.5 for Windows.

### Results

As shown in Table 1, PBPC and BM groups had similar demographic and clinical characteristics, apart from extensive, chronic GVHD. This condition was more frequent in patients of the PBPC group.

Results of the WHOQOL-100, using the Wilcoxon's rank sum test (Table 2) were unfavorable in patients of the PBPC group in one domain (Level of independence) mainly due to mobility and daily life

**Figure 2. Probability of extensive chronic GVHD.**

activities, as well as in a few other facets. There was no difference between groups in the levels of anxiety and depression on the HAD scale.

According to the patients' spontaneous responses, 8 individuals (6 in the PBPC and 2 in the BM group) believed that their QOL had worsened. Seven of these patients (5 PBPC and 2 BM) had extensive chronic GVHD and 5 (3 PBPC and 2 BM) were on immunosuppressive treatment.

The *linear regression model* showed, in univariate analysis, relationships between PBPC and the following variables: pain and discomfort ( $p=0.03$ ,  $R^2=0.18$ ), level of independence ( $p=0.04$ ,  $R^2=0.15$ ), mobility ( $p=0.01$ ,  $R^2=0.21$ ) and activity of daily living ( $p=0.01$ ,  $R^2=0.21$ ); and for extensive chronic GVHD: bodily image and appearance ( $p=0.01$ ,  $R^2=0.22$ ), level of independence ( $p=0.04$ ,  $R^2=0.16$ ) and health and social care - accessibility and quality ( $p=0.009$ ,  $R^2=0.25$ ). The multivariate analysis did not show a statistical significance for any of the variables analyzed. The comparison of the probabilities of extensive chronic GVHD in both groups is shown in Figure 2; chronic GVHD was more common among recipients of PBPC ( $p=0.006$ ).

### Discussion

In spite of the small number of patients, the present study is distinct from most, if not all, others as it provides QOL data from a randomized controlled trial comparing patients treated with BM or PBPC transplantation. Our findings suggest that QOL scores were unfavorable to PBPC patients in the Level of Independence domain in the facets of Mobility ( $p=0.02$ ) and Daily Living Activities ( $p=0.03$ ). Most patients who reported that their QOL had worsened had extensive chronic GVHD

and were in the PBPC group.

Among some methodological limitations of the study, the small sample size is a very significant weakness. This has restricted the nature of the statistical analyses performed, as well as increasing the risk of type II errors. On the other hand, with the end of our original randomized study<sup>15</sup> no additional subjects would be available for analysis at a later time. As there was no BMT-specific instrument, such as the FACT-BMT, validated in the country, we decided to use standard and widely used instruments to test whether alternative treatment procedures exert differential effects on post-transplantation QOL. Another limitation was the fact that the follow-up range was very broad (444-1997 days). It is unfortunate that all patients were not surveyed before the BMT and at the same and several periods of the follow-up time, in order to offer some sense of the QOL along time in the two groups. The loss to follow-up of the 30 patients who died also limits the generalizations that can be drawn from the findings.

Chiodi *et al.*<sup>5</sup> and Yano *et al.*<sup>6</sup> report that a shorter time from transplant and the presence of chronic GVHD are associated with poor QOL, independently of graft source. In the present study poor QOL related to the graft source of cells only in the area of physical performance. The median follow-up was shorter in PBPC recipients than in BM recipients: although not significant, the longer follow-up could have favored better QOL in BMT recipients. While this did not yield a statistically significant difference, it might have been large enough to account for a significant portion of the variance in QOL outcomes observed between the groups.

The incidence and severity of chronic GVHD seem to be the most important problems linked to PBPC transplant, and the majority of controlled and randomized trials have shown that the incidence and severity of cGVHD are higher in patients transplanted with PBPC.<sup>7,8,11,14</sup> The studies regarding acute GVHD do not show general agreement. Some authors suggest an increase in the frequency and severity of acute GVHD<sup>11</sup> and others do not.<sup>7,8,9,10,12-14</sup> The physiology of this important complication is not completely known and much research is ongoing in order to understand this disease.

Overall, our findings do not support the hypothesis that the two forms of treatment differ in their impact on QOL. However they suggest that QOL seems to be negatively affected by PBPC grafting in an area related to the ability of the patient to perform daily living activities with no pain and discomfort. This is probably due to the frequency and

severity of chronic GVHD. Reduced QOL in allogeneic peripheral blood recipients has already been reported by others.<sup>24</sup> In light of the small sample size and the substantial loss of follow-up, larger studies should address the link between PBPC transplantation, chronic GVHD, immunosuppression treatment and their impact on the QOL.

In conclusion, overall QOL was reduced in patients receiving PB as compared to in those receiving BM allografts. This is probably due to the frequency and severity of chronic GVHD. Due to the small number of patients not all comparisons were statistically significant. We believe our study warrants QOL analyses of the large international PBPC vs BM randomized trials.

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*CAdS and NJB were the principal authors. They were primarily responsible for this paper from the conception until submission of the manuscript. The remaining authors qualified for authorship according to the World Association of Medical Editors (WAVE) and have taken specific responsibility for the following parts of the content: MD and ACV designed the article, drafted and revised it critically for important intellectual content; FJPA, GBO, and KABE collected, analyzed, and interpreted the data; RZ and ECMM were responsible for the statistical analyses. All these contributors have discussed and agreed with the final version of the paper. CAdS was responsible for all the Tables and Figures.*

#### *Disclosures*

*Conflict of interest: none.*

*Redundant publications: no substantial overlapping with previous papers.*

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## PEER REVIEW OUTCOMES

### Manuscript processing

This manuscript was peer-reviewed by two external referees and by Dr. Andrea Bacigalupo, who acted as an Associate Editor. The final decision to accept this paper for publication was taken jointly by Dr. Bacigalupo and the Editors. Manuscript received March 6, 2002; accepted October 16, 2002.

### What is already known on this topic

There is very little in the literature on quality of life after allogeneic transplantation, especially when comparing two different sources of stem cells. This is what makes this study interesting.

### What this study adds

The study adds to our understanding of long-term complications of allogeneic stem cell transplants. Peripheral blood is often preferred because of rapid engraftment. This study suggests that we should also consider long-term sequelae, and chronic GvHD, which is increased after allogeneic PB grafts, may significantly impair the quality of life.

### Potential implications for clinical practice

The implications are that for patients with early disease (first remission of acute leukemia and first chronic phase of chronic myeloid leukemia, as well as for non malignant diseases such as aplastic anemia and thalassemia) bone marrow remains the preferred source, because results are good and chronic GvHD limited. For patients with advanced disease one may opt for peripheral blood with the understanding that there is a higher risk of long-term complications. Alternatively T-cell depletion of peripheral blood grafts (either *in vivo* or *ex vivo*) must be taken into considerations.

Andrea Bacigalupo, Associate Editor  
(Genoa, Italy)