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Health-Related Quality of Life in leukemia Survivors of Allogeneic Hematopoietic Stem Cell Transplantation Employing the Mexican Reduced-Intensity Conditioning

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ABSTRACT

Background: Quality of life (QOL) is an important consideration in the counseling, implementation, and post-treatment management of arduous treatments for life-threatening conditions such as allogeneic hematopoietic cell transplantation (allo-HCT). **Objective:** To analyze the QOL of leukemia patients allografted with the Mexican reduced-intensity conditioning regimen in two Mexican academic medical centers. **Material and methods:** By means of the quality metric short form 36 version 2 to measure generic health concepts, relevant QOL was analyzed in leukemia patients who underwent allo-HCT using reduced-intensity conditioning on an outpatient basis at either the Centro de Hematología y Medicina Interna de Puebla of the Clínica Ruiz or the Hematology Service of the Internal Medicine Department of the Hospital "Dr. José Eleuterio González" of the Universidad Autónoma de Nuevo León, and who had survived more than 12 months after the allograft, who could be approached, who were in a continued complete remission (with or without graft-versus-host disease), and who were willing to respond to the questionnaire. Thirty-five patients fulfilling these requirements were included, and a sex- and age-matched group of 35 reference subjects was also studied. **Results:** Allografted patients were found to have a slightly better mental component summary than the reference subjects (53.23 vs. 48.66 points; p = 0.01), whereas the physical component summary did not show a difference (54.53 vs. 52.05 points; p = 0.59). Most of the differences between allografted individuals and reference subject controls were not significant. **Conclusions:** Despite several sources of bias, these data suggest that allografted individuals employing the Mexican reduced-intensity conditioning regimen enjoy a health-related QOL life similar to that of reference subjects, adding another advantage of this method of conducting stem cell allografts. However, more work needs to be done to elucidate the impact of reduced-intensity conditioning on post allo-HCT QOL. (REV INVES CLIN. 2015;67:109-16)
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Key words: Quality of life. Health-related quality of life. Allograft. Reduced intensity. Stem cell transplant.

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INTRODUCTION

Quality of life (QOL) is a dynamic concept related to physical, cognitive, emotional, social functioning and well-being. Cancer survivors routinely cite issues related to QOL as amongst their greatest concerns[1]. Quality of life is an especially important consideration in the counseling, implementation, and post-treatment management of arduous treatments for life-threatening conditions, such as allogeneic hematopoietic cell transplantation (allo-HCT), which is an effective and potentially curative treatment for a variety of hematological diseases[2]. However, allo-HCT carries a significant risk of acute complications and late effects, which include chronic graft-versus-host disease (GVHD), organ toxicity, osteoporosis, infections, cataracts, secondary cancers, and infertility, as well as decreased QOL[1,2].

Reduced-intensity conditioning (RIC) has been developed to decrease the regimen-related toxicity of allo-HCT and to induce host-versus-graft transplant tolerance with rapid engraftment of donor stem cells, subsequently diminishing GVHD. Reduced-intensity conditioning is appropriate for the elderly and other high-risk patients who are otherwise ineligible to receive conventional allografts[2]. Acute complications and late undesired effects of an allograft are considerably less frequent and less severe after RIC than after conventional myeloablative conditioning[2,3].

We analyzed the QOL of a group of patients with leukemia who received an allograft after employing a uniform RIC method in an effort to define the salient features of QOL after RIC allografting.

PARTICIPANTS AND METHOD

Participants

Data was analyzed from leukemia patients who underwent peripheral blood hematopoietic stem cell (PBSC) allografts using RIC on an outpatient basis at either the Centro de Hematología y Medicina Interna de Puebla of the Clínica Ruiz or the Hematology Service of the Internal Medicine Department of the Hospital Universitario "Dr. José Eleuterio González" of the Universidad Autónoma de Nuevo León between October 1988 and November 2011.

Stem cell transplantation

Reduced-intensity conditioning was used in all patients[2,3]. A Karnofsky score of 100% was required to conduct the allograft. In all instances, the donor was a sibling with compatible (5/6) or identical (6/6) human leukocyte antigens. The Institutional Review Board and the Ethics Committee of both institutions approved the study protocol. Written consent was obtained from all patients. Subcutaneous granulocyte-colony stimulating factor (10 μg/kg/day) was given to the sibling donors on days −5 to +2, and one to three aphaeresis procedures were planned for days 0, +1 and +2 using a Haemonetics V50 PLUS System (Haemonetics Corporation, Braintree, MA), a Baxter C-3000 PLUS machine (Baxter Healthcare, Deerfield, IL), an AMICUS (Baxter Healthcare, Deerfield, IL), or a COBE-Spectra (Gambro, Lakewood, CO) device using the Spin-Nebraska protocol[2,3]. The endpoint of collection was the processing of 5,000-7,000 ml of blood/m^2 in each aphaeresis procedure, providing a total amount of at least 2×10^6 viable $CD34^+$ cells/kg of body weight of the recipient. The non-ablative conditioning used in this study consisted of the following[9]: oral busulphan 4 mg/kg given on days −6 and −5; cyclophosphamide 350 mg/m^2 IV on days −4, −3 and −2; and fludarabine 30 mg/m^2 IV on days −4, −3 and −2. Patients received chemotherapy at the outpatient clinic and were discharged after the procedure. All patients were examined daily at the outpatient transplant clinic until engraftment, and had a caregiver at home or in a temporary residence (relative or friend) who took care of food preparation, assisted in personal hygiene, controlled the scheduling and dosage of prescribed oral medication, and was alert to any complication that required medical attention. Oral cyclosporin A (CsA) was administered at 5 mg/kg starting on day −1. In all patients methotrexate 5 mg/m^2 IV was given on days +1, +3, +5 and +11, CsA was continued through day 180, with adjustments made to obtain serum CsA levels of 150-275 ng/ml, and then tapered over 30-60 days. If GVHD was present, CsA was tapered over a longer period. Ondansetron (1 mg IV every hour for four hours after IV chemotherapy), and ciprofloxacin (500 mg twice daily), fluconazole (100 mg once daily) and acyclovir (400 mg twice daily) were used in all patients until neutrophil counts were > 500×10^6/l for three consecutive days. The PBSC aphaeresis products were infused on days 0 to +1. Chimerism

was assessed in cases involving a sex mismatch with a fluorescent *in situ* hybridization technique to mark the X and Y chromosomes[2,3]. In cases with an ABO mismatch, a flow cytometry-based approach was used, while polymorphic markers (short tandem repeats)[2,3] were analyzed in the absence of any mismatch. The procedure was to be conducted on an outpatient basis in all cases; however, hospital beds were kept available for those patients needing admission.

Assessment of quality of life

The quality metric SF-36v2 developed by Syrjala, et al.[4] during the Medical Outcomes Study to measure generic health concepts relevant across age, disease, and treatment groups as well as validated with a recall period of four weeks (standard version) was chosen: this is a generic questionnaire with 36 questions that has two components and eight domains. The questionnaire was translated into Spanish. This instrument was selected because of the previous expertise of the researchers with its use and because it is a set of generic, coherent, and easily administered QOL measures, now widely utilized by managed care organizations for routine monitoring and assessment of care outcomes in patients. The two components are the physical component summary and the mental component summary. The physical component is divided into four domains: physical function, physical role, bodily pain, and general health, while the mental component forms part of these four domains: mental health, emotional role, social function, and vitality. Each domain was examined by comparing the allografted patients with the reference group. Stata® basic statistics was used employing the Mann-Whitney-Wilcoxon rank sum test, a non-parametric test of the null hypothesis that tests if two populations are the same against an alternative hypothesis. This test allows two data samples that are independent if they come from distinct populations and the samples do not affect each other; it defines whether the population distributions are identical without assuming them to follow the normal distribution. The specific questions of this instrument are included in the appendix. The study was reviewed and approved by the Institutional Review Board and Ethics Committee of both institutions, and informed written consent was obtained from both the patients and the reference subjects.

RESULTS

Patients, reference subjects and allografts

Individual telephone or personal interviews were attempted in all the patients with leukemia, allografted between October 1988 and November 2011 in the two institutions, who had survived more than 12 months after the allograft, who could be approached, who were in a continued complete remission (with or without GVHD), and who were willing to respond to the questionnaire. A total of 156 patients with leukemia were allografted in that period and 62 of them were alive. Of these, 22 could not be reached and five did not accept to take the questionnaire. As a result, 35 individuals fulfilling all these requirements were included in the study; there were 15 patients with chronic myelogenous leukemia, 10 with acute myelogenous leukemia, eight with acute lymphoblastic leukemia, and two with chronic lymphocytic leukemia. Median age was 44 years (range, 18-70), 18 males and 17 females. A reference group of 35 persons, age and sex matched, was selected between normal volunteers, all of them healthy healthcare workers; in this group, median age was 44 years (range, 18-70), and there were also 18 males and 17 females. Comorbidities were recorded in 20 of 35 allografted patients: GVHD in six (three acute and two chronic), hypothyroidism in three, type 2 diabetes in three, obesity in three, femoral vascular necrosis in two, and depression, hearing impairment, herpes, Sjogren's syndrome and rheumatoid arthritis in one each. All patients received PBSC allografts. The conditioning regimen was delivered as an outpatient procedure in all individuals. None of the patients were given radiotherapy or antithymocyte globulin during the conditioning. Of the 35 patients, 29 were never admitted to the hospital, while six were admitted due to grade III-IV acute GVHD, fever, or mucositis. Patients were followed for periods ranging from 12 to 215 months (median, 27). Patients with chronic GVHD received low doses of steroids.

Assessment of quality of life

Table 1 and figure 1 summarize the salient features of the allografted patients and the reference group:

– Allografted patients were found to have a slightly better, non-significant mental component summary than the reference group (53.23 vs. 48.66 points;

Table 1. Salient features of allografted patients and reference subjects

	Patients	Reference subjects	p value
Number	35	35	1.00
Age in years, median (range)	45 (18-70)	45 (18-70)	1.00
Female %	48%	48%	1.00
QOL dominions:			
– Physical component:	52.05	54.537	0.59
• Physical function	86.29	93.14	0.52
• Physical role	77.86	91.43	0.24
• Bodily pain	80.71	82.06	0.71
• General health	71.57	65.23	0.20
– Mental component:	53.23	48.66	0.010*
• Vitality	73.04	59.29	0.006*
• Social function	79.64	81.07	0.23
• Emotional role	86.69	86.67	0.60
• Mental health	82.71	74.57	0.007*
Diagnosis:			
– AML	10	—	
– ALL	8	—	
– CML	15	—	
– CLL	2	—	
Comorbidities:			
– None	42%	—	
– Hypothyroidism	8%	—	
– Diabetes mellitus type 2	8%	—	
– Obesity	8%	—	
– Acute GVHD	8%	—	
– Chronic GVHD	5%	—	
– Avascular femoral head necrosis	5%	—	
– Dyslipidemia	5%	—	
– Pulmonary fibrosis	3%	—	
– Depression	3%	—	
– Hearing loss	3%	—	
– Herpes	3%	—	
– Sjögren's syndrome	3%	—	
– Rheumatoid arthritis	3%	—	

*Significant differences.
QOL: quality of life; AML: acute myelogenous leukemia; ALL: acute lymphoblastic leukemia; CML: chronic myelogenous leukemia; CLL: chronic lymphocytic leukemia; GVHD: graft-versus-host disease.

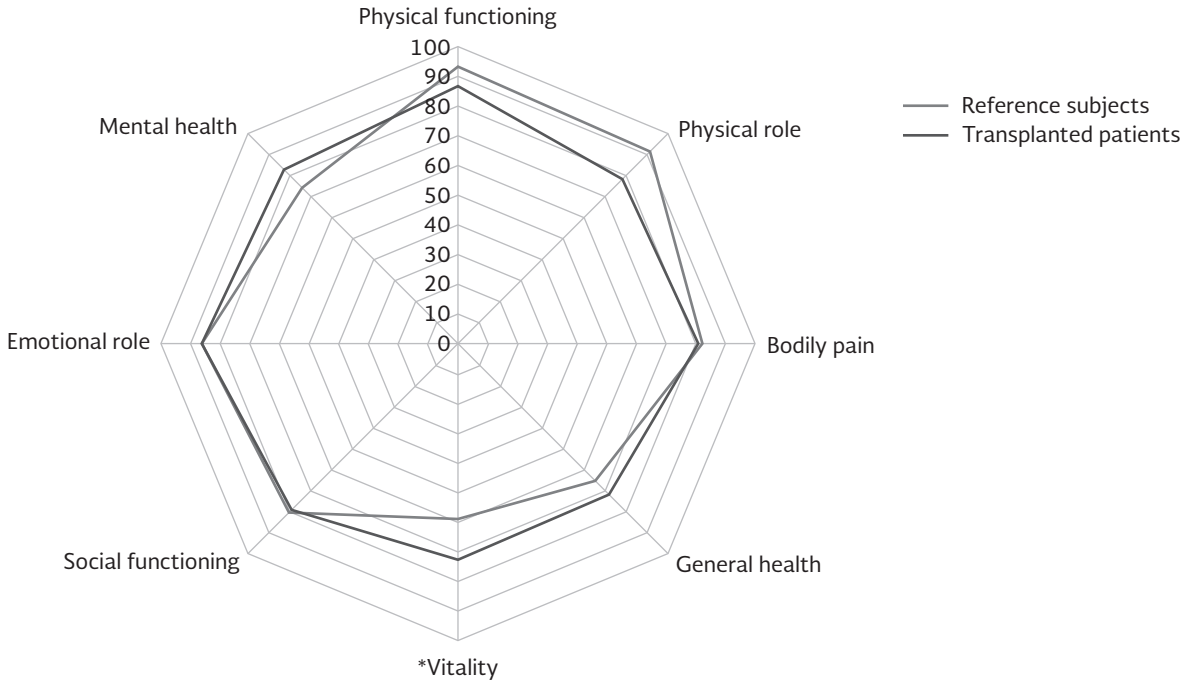
p = 0.010), whereas the physical component summary was better in the reference group (54.53 vs. 52.05 points; p = 0.59) (Fig 1).

– Within the physical component, allografted patients had a non-significant better general health score than the reference subjects (71.57 vs. 65.23 points; p = 0.20), a worse non-significant physical function than the reference group (86.29 vs. 93.14 points; p = 0.52), a worse non-significant physical role (77.86 vs. 91.43 points; p = 0.24), and a worse non-significant bodily pain score (80.71 vs. 82.06 points; p = 0.71).

– Within the mental component, allografted patients had a better vitality than the controls (73.04 vs. 59.29 points; p = 0.006), a better mental health score (82.71 vs. 74.57 points; p = 0.007), a better non-significant emotional role score (86.69 vs. 86.67 points; p = 0.60), and a worse non-significant social function (79.64 vs. 81.07 points; p = 0.23).

Most of the above mentioned differences were not statistically significant. In the analysis of the group of allografted individuals, other statistically significant differences were found: females had a better QOL than males in the following categories: physical role (92.28 vs. 77.43; p = 0.0001), general health (70.18 vs. 66.72; p = 0.002), vitality (70.59 vs. 61.98; p = 0.056), and physical component summary (53.78 vs. 52.84; p = 0.0001). Males had better QOL

Figure 1. Radial graph of scores for quality of life for transplanted patients and reference subjects.
*Significant differences.



than females in physical function (90.56 vs. 88.82; p = 0.093) and social function (82.29 vs. 78.31; p = 0.0001). There were no differences in QOL regarding the variant of the leukemia. Single individuals enjoyed a better QOL than married ones in general health (73.79 vs. 61.42; p = 0.043) and marginally significant emotional role (92.54 vs. 72.97; p = 0.666). Individuals transplanted before 2004 (1998-2011) had a significantly better QOL in physical function (93.75 vs. 82.39; p = 0.59) and physical role (100.0 vs. 66.30; p = 0.13), vitality was marginally significant (86.98 vs. 65.76; p = 0.66), emotional role (97.92 vs. 80.83; p = 0.024), the physical component (56.17 vs. 49.90; p = 0.048) and mental component (58.15 vs. 50.66; p = 0.048).

Taken together, all these data suggest that allografted individuals receiving our RIC regimen enjoy a health-related QOL similar to or even better than that of the reference subjects.

DISCUSSION

High-dose therapy with allo-HCT offers effective control and potential cure of hematopoietic malignancies, but with the cost of associated morbidity that includes adverse effects on QOL. A growing body of literature has characterized this impact; longitudinal studies suggest early moderate impairments that largely return to pretransplantation levels by day 100; the majority of studies suggest that more than 60% of patients report good-to-excellent QOL in years 1-4 after HCT[1]. Cross-sectional studies suggest larger and more persistent decreases in QOL in comparison with matched non-cancer controls and population normative data[1], contrary to what was found in this study. Acute and chronic GVHD have been identified as significant threats to QOL[1,2].

The use of RIC for allo-HCT is based on the immune-mediated allogeneic graft-versus-tumor effect. The procedure was initially developed for patients who could not tolerate the intense bone marrow ablation used in conventional transplantation methods. In developing countries, conventional transplantation using special inpatient transplantation units and standard myeloablative conditioning regimens is unaffordable for most patients[5]. To overcome this problem, in the last years we have implemented changes in the therapeutic approach, which has resulted in the simplification of conducting allografts. The use of RIC regimens for allografting by our group[5,6] and others[7] has resulted

in a substantial reduction in costs, and since the cost of grafting PBSC is lower than the cost of allografting using bone marrow-derived stem cells, we have chosen to always employ PBSC. In addition to lowered costs, RIC allografting, in our experience, has resulted in diminished transplant complications: less incidence and severity of GVHD[2,8], less renal toxicity[9], less reactivation of cytomegalovirus infection[10,11], less incidence of opportunistic infections[5,6], less incidence of seizures and neurologic complications[12], and less incidence of secondary neoplasms[13]. We consider that these diminished toxicities stem mainly from the magnitude of the damage to both the hematopoietic and the immune systems; however, other mechanisms can also account for these differences, such as the outpatient conducting of the transplants in most cases[5,8]. The literature examining the impact of RIC allografting on QOL is limited and deserves further exploration. Overall, studies suggest that QOL after RIC is good[14] and comparable with that seen with myeloablative conditioning[15] as well as autologous HCT[16]. Patients receiving RIC allografts appear to have an immediate QOL advantage over autologous patients, but this advantage may be reversed 3-6 months after transplantation[16]. These comparisons, however, may be confounded by patient factors that influence the decision to use RIC regimens[1]. Along this line, it is also possible that both the diminished toxicity of the Mexican RIC schedule and the outpatient conducting of the allografts lead to a less severe modification of the health-related QOL, as shown in the information that we are presenting here. It is interesting to mention that the health-related QOL of acute myeloid leukemia survivors, given or not stem-cell transplants, is worse than that in the general population[17] and apparently worse than that of survivors of stem-cell allografts employing the Mexican RIC method. It is also worthwhile mentioning that the apparent advantage in certain points of the QOL of the allografted patients may be influenced by the fact that, as this is a self-assessment instrument, individuals overcoming life-threatening experiences such as the diagnosis of leukemia, the chemotherapy, and the allograft, may be more satisfied with their QOL than those in the reference group. Other sources of bias have to be mentioned as well: the population in this cohort represents a very heterogeneous group, some of them one year after transplantation and others up to 17 years; the patients who were not reached may be the ones who are struggling the most post-transplantation; the patients who agreed to participate may likely be the ones with the best QOL; chronic GVHD was present in a very small subset of the patients included and it is well known that chronic GVHD is the predominant determinant of long-term QOL post-transplantation, etc.

Be that as it may, in conclusion, we have found that allografted individuals employing the Mexican RIC regimen after 12 months enjoy a health-related QOL similar to that of reference subjects, with this being another advantage of this method of conducting stem-cell allografts. It has to be emphasized that this is a retrospective pilot study in a small subset of patients that may not represent all the patients who have survived more than one year after the allograft employing the Mexican approach. It is clear that more work needs to be done to elucidate the impact of RIC on post-HCT QOL.

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APPENDIX

Physical health

Physical function
(Limited a lot, limited a little, not limited at all)
– Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports
– Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf
– Lifting of carrying groceries
– Climbing several flight of stairs
– Climbing one flight of stairs
– Bending, kneeling, or stooping
– Walking more than a mile
– Walking several hundred yards
– Walking one hundred yards
– Bathing or dressing yourself

Physical role
During the past four weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?
(All of the time, most of the time, some of the time, a little of the time, none of the time)
– Cut down on the amount of time you spent on work or other activities?
– Accomplished less than you would like?
– Were limited in the kind of work or other activities?
– Had difficulty performing the work or other activities (for example, it took extra effort)?

Bodily pain
– How much bodily pain have you had during the past four weeks?
  (None, very mild, mild, moderate, severe, very severe)
– During the past four weeks, how much did pain interfere with your normal work including both work outside the home and housework?
  (Not at all, a little bit, moderately, quite a bit, extremely)

General health
– In general, would you say your health is:
  (Excellent, very good, good, fair, poor)
– Compared to a year ago, how would you rate your general health?
  (Much better now than one year ago, somewhat better now than one year ago, about the same as one year ago, somewhat worse now than one year ago, much worse now that one year ago)

How TRUE or FALSE is each of the following statements for you
(Definitely true, mostly true, don't know, mostly false, definitely false)
– I seem to get sick a little easier than other people
– I am as healthy as anybody I know
– I expect my health to get worse
– My health is excellent

Mental health

Vitality
(All of the time, most of the time, some of the time, a little of the time, none of the time)
– Did you feel full of life?
– Did you have a lot of energy?
– Did you feel worn out?
– Did you feel tired?

Social function
– During the past four weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?
  (Not at all, slightly, moderately, quite a bit, extremely)
– During the past four weeks, how much of the time has your physical health or emotional problems interfered with your social activities, like visiting friends, relatives, etc.?
  (All of the time, most of the time, some of the time, a little of the time, none of the time)

Emotional role
During the past four weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?
(All of the time, most of the time, some of the time, a little of the time, none of the time)
– Cut down on the amount of time you spent on work or other activities?
– Accomplished less than you would like?
– Did work or activities less carefully than usual?

Mental health
(All of the time, most of the time, some of the time, a little of the time, none of the time)
– Have you been very nervous?
– Have you felt so down in the dumps that nothing could cheer you up?
– Have you felt calm and peaceful?
– Have you felt downhearted and depressed?
– Have you been happy?