

Functional evaluation indicates physical losses after hematopoietic stem cell transplantation

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Objective: To perform a function evaluation of patients before and after hematopoietic stem cell transplantation.

Methods: From November 2008 to November 2010, 29 female (58%) and 21 male patients (42%) with median age of 48 years (range: 24-67) were enrolled in this study. Data collection was performed before and after autologous or allogeneic hematopoietic stem cell transplantation. Evaluation instruments included the 2-minute walking test to evaluate gait performance with assessment of the oxygen saturation, heart rate and Borg Scale before and after the test; grip strength for strength evaluation, Schober Test for spine mobility testing and maximum and adapted activity scores of the Human Activity Profile questionnaire to test functionality in daily activities.

Results: Fifty patients were evaluated at baseline; six did not undergo hematopoietic stem cell transplantation (three died, one refused and two were excluded). Thus 44/50 (88% - 21 allogeneic and 23 autologous) transplantations were performed. Only 33 of the 44 patients (75%) performed evaluations after transplantation (nine died and two were excluded). Of the patients who performed both evaluations, significantly lower values were found in the evaluation after transplantation for the 2-minute walking test (p -value = 0.004), grip strength of both right and left hands (p -value = 0.004 and p -value < 0.0001, respectively), the Schober Test, and maximum and adapted activity scores (p -value < 0.0001). The heart rate was higher (p -value = 0.01) before the 2-minute walking test and oxygen saturation was higher (p -value = 0.02) after.

Conclusion: Statistical differences indicate functional impairment after transplantation showing physical losses in this population.

Keywords: Rehabilitation; Physical examination; Hematopoietic stem cell transplantation

Introduction

Hematopoietic stem cell transplantation (HSCT) is widely used for the cure of a variety of hematological malignant and non-malignant diseases, metabolic diseases and immunological disorders. The conditioning regimen, isolation, restriction of activities and complications that might occur in this procedure provoke significant psychic, physical and psychosocial distress^(1,2). When returning to their daily living activities, many patients complain about fatigue, worsening functionality and reduced participation in activities that may require physical effort such as work, recreation and domestic activities^(3,4).

The most commonly reported functional deficits in this population are fatigue⁽⁵⁻⁷⁾, lost of physical performance^(8,9) and loss of muscle strength^(5,10-13). Clinical events such as mucositis, acute and chronic graft versus host disease (GVHD), nutrition disorders, infections, emotional problems and stress may culminate in worse physical and psychological conditions^(14,15).

Functions associated to physical capacity are a useful indicator of good health and longevity when related to disease processes; this is the main target of rehabilitation^(16,17). Functional measures are commonly used in epidemiologic studies of incapacity and in the evaluation of rehabilitation programs. They are considered important variables for clinical research and can provide supplementary information for medical diagnosis⁽¹⁸⁾.

Function capacity is directly linked to physical status and is the most important domain to be considered in quality of life (QOL)⁽¹⁹⁾. Functional evaluations can be used to assess many physical aspects such as aerobic conditioning^(6,14,16,20), muscle strength^(5,12,20-22), functional capacity^(6,8,12,23), mobility⁽¹⁶⁾ and QOL^(7,23-25).

There is a variety of measures and tools available to carry out functional evaluations which involve different domains. These range from ability and physical skill tests (walking tests, treadmill tests, strength tests, mobility tests, etc) to self-report questionnaires (to evaluate specific areas – such as pain and daily life activities - or general health related status – such as the quality of life short form 36 questionnaire), and self-reports related to psychic conditions.

The aim of this study was to prospectively evaluate all domains of physical capacity that interfere in functionality before and after HSCT.

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Methods

Selection of subjects

This prospective study enrolled all consecutive patients between 18 and 70 years old with malignant hematological diseases, who underwent autologous or allogeneic HSCT at the HSCT unit of the Hospital das Clinicas of the Universidade Estadual de Campinas – UNICAMP from November 2008 to November 2010. The patients were included if they were submitted to high-dose or reduced-dose allogeneic HSCT with HLA-identical related donors with cells harvested from bone marrow or peripheral blood. The conditioning regimens and prophylaxis for GVHD were selected according to existing protocols at the University Hospital.

The exclusion criteria were previous HSCT and non-malignant, neurologic, psychiatric and orthopedic diseases. Four patients were not included in the study: two were diagnosed with depressive disorder, one was submitted to lower limb amputation and one did not agree to participate in the study. All consecutive patients who met the inclusion criteria and that agreed to participate in this study gave their written informed consent. The protocol was designed in accordance with the requirements for research involving human subjects and approved by the Institutional Review Board (protocol number 784/2008).

For cases of fever, infection, severe thrombocytopenia and neutropenia at the time of evaluation, the tests were postponed, when possible, until after the patient had recovered. Any conditions that contraindicate exercise or those specified in the guidelines for the six-minute walking test of the American Thoracic Society⁽²⁶⁾ were also considered for the two-minute walking test (2MWT).

Study procedure

Data collection and the evaluation of functions were performed before HSCT (Phase 1) and after discharge on an outpatient basis (Phase 2). Anthropometric data were collected and the body mass index (BMI) was calculated. The instruments used in the evaluation were: 1. the 2MWT, an evaluation of walking capacity performed on a 20-meter indoor track to evaluate function of gait performance and aerobic conditioning; 2. oxygen saturation (SaO₂); 3. heart rate (HR) assessed by a pulse oximeter; 4. the Borg Scale (BS), a 0 to 10 scale of fatigue sensations, to assess fatigue before and after the 2MWT; 5. grip strength test (GS) for hand strength evaluation, performed three times for each hand with small intervals between, using a hand hydraulic dynamometer; 6. the Schober Test (ST), a flexion trunk test to evaluate lumbar spine mobility; 7. maximum and adapted activity score (MAS and AAS), variables of the Human Activity Profile (HAP) questionnaire that evaluate functioning related to daily life activities with the energy expenditure needed for each activity.

Statistical analysis

Descriptive analyses were performed for all variables. The paired sample t-test was applied for physical and functional variables to assure that the means represent the same group at different times. The independent sample t-test was used to compare the type of HSCT. P-value < 0.05 was considered significant and the SPSS (Statistical Package of Social Sciences) version 14.0 was used for data analysis.

Results

As intention to treat, 50 patients were enrolled in the present study. The median age was 48 (24-67) years and 29 (58%) of the patients were female. Forty-four out of 50 (88%) patients underwent HSCT [21 (48%) allogeneic and 23 (52%) autologous]. Six of 50 (12%) patients were not submitted to HSCT as three died before the procedure, one refused to participate due to complete remission before HSCT and two were excluded; one had exclusion criteria and the other due to an unacceptable donor. Data on the patients and HSCT characteristics are shown in Table 1.

Table 1 - Patients and transplant characteristics (n = 50)

Variable	
Age (years) - mean ± SD/median (range)	46 ± 13 / 48 (24-67)
Gender (male/female) - n	21 / 29
Weight (kg) - mean ± SD/median (range)	70 ± 19 / 66.8 (35-121.6)
Height (m) - mean ± SD/median (range)	1.65 ± 13 / 1.7 (1.2-1.9)
BMI (kg/m ²) - mean ± SD/median (range)	25.7 ± 6.2 / 24.8 (15.8-44)
Diagnosis at transplant - n	
Acute Leukemias	16
Lymphomas	17
Myelomas	8
Others	9
Pre-transplantation risk category - n	
Low risk	15
High risk	35
Transplant type (n)*	
Autologous	23
Allogeneic	21
Conditioning regimen type - n	
Autologous HSCT	
BEAM	13
Melphalan	8
Bu + CY	2
High dose – Allogeneic HSCT	
Bu + CY	6
Bu + CY + VP	3
ICT + CY + VP	1
Bu + Fludarabine	1
Reduced Intensity – Allogeneic HSCT	
TBI + Fludarabine	2
Melphalan + Fludarabine	8
GVHD prophylaxis - n	
MTX + CsA	19
MMF + CsA	2
Months from diagnosis to HSCT - median (range)	
Autologous HSCT	20 (6-211)
Allogeneic HSCT	5 (2-123)

SD: standard deviation; BMI: body mass index; Others: 3 chronic lymphocytic leukemia, 3 myelodysplastic syndrome and 1 myelofibrosis (myeloproliferative disorders), 2 chronic myeloid leukemia (CML); Low risk: complete remission or chronic phase CML; High risk: partial remission, relapse, progression, accelerate phase for CML; BEAM: carmustine, etoposide, cytarabine and melphalan; Bu: busulfan; CY: cyclophosphamide; VP: etoposide; TBI: total body irradiation; GVHD: graft versus host disease; MTX: methotrexate; CsA: cyclosporine; MMF: mycophenolate mofetil

*Six patients did not perform transplant

Thirty-three of 44 (75%) patients performed evaluations in Phase 1 (before) and Phase 2 (after HSCT). Eleven (25%) patients did not complete the Phase 2 evaluations as nine died and two were excluded due to physical and clinical impairment. Figure 1 shows the flowchart of patients' distribution for phase 1 and phase 2. The Phase 1 functional evaluation of patients who died after HSCT and thus did not perform the Phase 2 evaluation, was not statistically different compared with those who performed both evaluations.

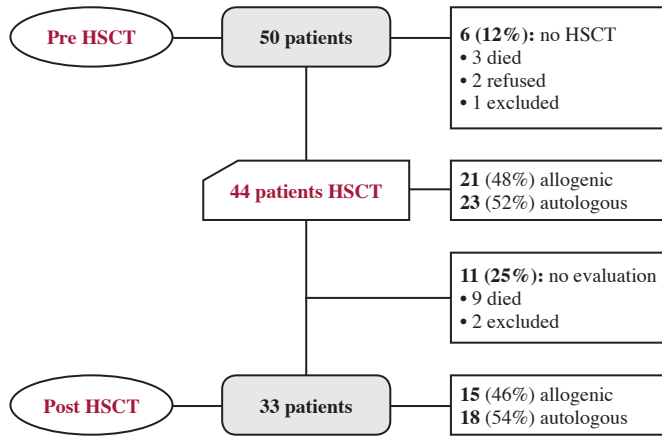


Figure 1 - Flowchart showing patient distribution before and after HSCT

The Phase 1 functional evaluation was compared between allogeneic and autologous HSCT patients and the functional status was statistically similar (Table 2).

For the 33 patients who performed both evaluations, 18 patients underwent autologous and 15 underwent allogeneic HSCT. When the transplant outcomes were analyzed for patients who performed both Phase 1 and Phase 2 functional evaluations, the median length of total parenteral nutrition (TPN), the length of antibiotic therapy, and time to neutrophil and platelet engraftment were longer in the allogeneic HSCT group, resulting in a longer hospital stay. The transplant outcomes are presented in Table 3.

Functional outcomes comparing Phase 1 and Phase 2 evaluations

The median time in days from the Phase 1 evaluation to HSCT was 26 days (range: 7-188) and from HSCT to Phase 2 evaluation was 41 days (range: 17-187). The expectation was to evaluate patients until 60 days after HSCT and only three patients exceeded this timeframe.

Of the patients who performed both evaluations, there were significantly lower values in Phase 2 for weight and BMI (p-value < 0.0001), 2MWT (p-value = 0.004), ST (p-value < 0.0001), GS for both right and left hands (p-value = 0.004 and < 0.0001, respectively), MAS and AAS (p-value < 0.0001 for both) and higher values for HR before 2MWT (p-value = 0.01) and SaO₂

Table 2 - Functional outcomes in Phase 1 for allogeneic and autologous hematopoietic stem cell transplantation (n= 44)

Outcomes	Type of HSCT		p-value*
	Allogeneic (n= 21)	Autologous (n= 23)	
Age (years) - median (range)	45 (25-65)	24 (24-67)	0.22
Gender (male) - n	11 (52)	9 (39)	0.54
Weight (kg) - median (range)	66.4 (35-121)	67.3 (43-113)	0.96
BMI (kg/m ²) - median (range)	24.9 (15.8-35.9)	24.6 (18.9-44.4)	0.84
Hemoglobin (g/dL) - median (range)	10.1 (7.0-14.8)	11.4 (6.9-15.2)	0.20
2MWT (meters) - median (range)	178 (113-224)	178 (107-224)	0.98
SaO₂			
Before 2MWT (%) - median (range)	98 (93-100)	99 (94-100)	0.92
After 2MWT (%) - median (range)	98 (91-100)	97 (91-100)	0.44
Heart rate			
Before 2MWT (bpm) - median (range)	87 (63-131)	79 (57-112)	0.18
After 2MWT (bpm) - median (range)	116 (73-152)	102 (69-143)	0.15
Borg score			
Before 2MWT, median (range)	0 (0-3)	0 (0-5)	0.66
After 2MWT, median (range)	3 (0-10)	2 (0-8)	0.12
Schober's test (cm) - median (range)	6 (2-10)	6 (2-9)	0.68
Grip Strength			
Right hand (kg) - median (range)	30.3 (14.7-55)	33.3 (19.0-56)	0.61
Left hand (kg) - median (range)	28.0 (14.0-47)	32.0 (16.0-49)	0.62
MAS - median (range)	53 (21-91)	56 (26-84)	0.15
AAS - median (range)	41 (-13-91)	48 (-1-82)	0.31

* p-value from independent-samples test;

HSCT: hematopoietic stem cell transplantation; BMI: body mass index; 2MWT: 2-minute walking test; SaO₂: oxygen saturation; bpm: beats per minute; MAS: maximum activity scale; AAS: adapted activity scale.

Table 3 - Transplant outcomes for patients who performed both evaluations (n= 33)

Outcome	Type of HSCT		p-value*
	Allogeneic (n= 15)	Autologous (n= 18)	
Mucositis II-III - n (%)	4 (26.6%)	12 (66.6%)	0.03
Mucositis IV - n (%)	8 (53.3%)	3 (16.6%)	
TPN, median (days) - median (range)	9 (0-16)	0 (0-8)	0.001
Antibiotics (days) - median (range)	11 (0-29)	7 (0-24)	0.11
Neutrophil engraftment (days) - median (range)	18 (11-26)	10 (8-13)	< 0.0001
Platelets engraftment (days) - median (range)	15 (11-40)	14 (11-20)	0.03
Days to discharge (days) - median (range)	25 (14-36)	15 (11-34)	0.001
Alive - n (%)	7 (47)	16 (89)	0.02

* P-value from independent-samples test;

TPN: total parenteral nutrition.

Table 4 - Functional outcomes for patients who performed both evaluation (n= 33)

Outcomes	Phase 1	Phase 2	P-value*
Weight (kg) - median (range)	67.3 (35-121.6)	64.8 (35.5-113.8)	< 0.0001
BMI (kg/m ²) - median (range)	26 (15.9-44.4)	23.8 (17.5-44.7)	< 0.0001
Hemoglobin (g/dL) - median (range)	11.1 (6.9-15.2)	10.7 (8.1-13.1)	0.09
2MW (m) - median (range)	181 (106-224)	165 (97-227)	0.004
SaO₂			
Before 2MWT (%) - median (range)	99 (95-100)	99 (92-100)	0.48
After 2MWT (%) - median (range)	97 (91-99)	98 (92-100)	0.02
Heart rate			
Before 2MWT (bpm) - median (range)	87 (57-131)	111 (70-152)	0.01
After 2MWT (bpm) - median (range)	96 (73-126)	123 (76-156)	0.20
Borg scale			
Before 2MWT - median (range)	0 (0-5)	3 (0-10)	0.06
After 2MWT - median (range)	1 (0-5)	3 (0-8)	0.74
Schober's test, median (range), cm	6.5 (2-9)	5.5 (1.5-9.5)	< 0.0001
Grip Strength			
Right hand (kg) - median (range)	31 (19-55)	31 (16-47)	0.004
Left hand (kg) - median (range)	31 (18-55)	27 (16-47)	< 0.0001
MAS - median (range)	54 (25-84)	42 (15-85)	< 0.0001
ASS - median (range)	45 (-1-81)	22 (-16-82)	< 0.0001

* P-value - Paired sample t-test

HSCT: hematopoietic stem cell transplantation; BMI: body mass index; SaO₂: oxygen saturation; bpm: beats per minute; MAS: maximum activity scale; AAS: adapted activity scale

after 2MWT (p-value = 0.02). No significant difference was found for HR after 2MWT, SaO₂ before 2MWT, Borg Scale before and after 2MWT and hemoglobin. The functional evaluation results comparing Phase 1 and Phase 2 are presented in Table 4.

Discussion

This study showed that patients acquire physical losses after autologous and allogeneic HSCT. The focus was on the physical components of function with the applied tools evaluating most of variables that compose physical capacity such as strength, aerobic conditioning, mobility, fatigue and QOL.

Fatigue and loss of strength in performing daily life activities are the first symptoms of functional deficit⁽⁵⁾. Cancer-related fatigue is described as one of the most prevalent and debilitating

side effects of cancer and its treatment⁽²⁷⁻²⁹⁾. In the current study, the 2MWT associated to oximetry and the adapted Borg Scale were used to assess aerobic conditioning and fatigue before and after exercise and the hand grip test to assess muscle strength. Although the origin of fatigue is considered multifactorial and its etiology is complex and not completely understood, common sense implies that it is strongly related to physical factors⁽³⁰⁾.

The 2MWT is a simple gait performance exam. Here it was demonstrated that this is a good instrument to evaluate gait performance in these patients; the results demonstrated impairment in walking after transplant. It is less encumbered by fatigue, but it demonstrates cardiopulmonary and musculoskeletal adaptations during gait performance⁽³¹⁾. The 2MWT was also reliable to evaluate other populations as a good indicator in the decline of function demonstrating gait performance^(32,33),

including patients with chronic GVHD⁽²⁰⁾. Although fatigue is a very common symptom after transplant, the Borg scale was not significantly different before and after transplant. However, the HR before 2MWT was higher. According to Gillis & Donovan⁽³⁴⁾ maintaining bed rest causes a chain of cardiac events that increases resting HR and provokes orthostatic intolerance with postural hypotension occurring due to the diminished blood volume and/or changes in autonomic responses. The increased HR before the 2 MWT found in our cohort of patients might be explained by bed rest.

The patients in this study presented reductions in spine mobility after HSCT. Muscle atrophy, restricted activities and being bedridden also have consequences on the overall range of motion. Schober's test is commonly used to evaluate lumbar spine mobility in patients with lumbar pain or lumbar joint impairment⁽³⁵⁾. Suesada et al.⁽³⁶⁾ investigated spine mobility in patients submitted to short-term hospitalization using the Stibor and Schober's tests and showed a decrease in mobility (p-value < 0.0001) which strongly suggests that only a short period of bed confinement is likely to reduce pelvic and spine mobility. As trunk flexion requires great joint mobility and muscle activation⁽³⁷⁾ this test gives an idea of whether or not the overall mobility is affected.

There was a statistically significant loss of weight and BMI in Phase 2 (p-value < 0.0001) and the grip test showed an important reduction in muscles of both hands after transplant. Chemotherapy, toxicities involved in HSCT and reduced food intake contribute to an energy imbalance that provokes loss of lean mass and weight⁽¹⁴⁾. Not only corticosteroids and chemotherapy induce fatigue, but also the neoplasia itself and the resulting production of inflammatory cytokines in the disease process⁽⁵⁾. In addition, oxidative stress from chemotherapy and radiation treatment, along with iron overload from multiple blood transfusions may contribute to muscle dysfunction through an excessive production of reactive species⁽¹¹⁾. White et al.⁽³⁸⁾ demonstrated that patients before HSCT had lower plasma concentrations of glutathione peroxidase, an important component of the circulating antioxidant system, compared with controls. Hence, muscle atrophy followed by strength loss and functional impairment are expected. Hand strength appears to be valid measurement to assess overall strength loss with this being confirmed by a great number of studies that investigated patients with other diseases and clinical conditions^(20,39-42).

One useful and widely used instrument with cancer patients is the QOL questionnaire. Courneya & Friedenreich, in a literature review about exercise and cancer, observed that all authors used some QOL instrument⁽¹⁹⁾ to evaluate the effect of interventions. The choice in this study was the HAP questionnaire. Created by Daughton et al.⁽⁴³⁾ this instrument evaluates functioning in daily life activities. It correlates 94 possible activities with the maximum consumption of oxygen needed to perform each activity. In this study there was a significant reduction in functioning as detected by the variables assessed by the HAP questionnaire (MAS and AAS). Herzberg et al.⁽⁸⁾ observed that, within one year of HSCT, the HAP was more sensitive to detect functional deficits resulting from chronic GVHD manifestations and steroid myopathy than the FACT-BMT and the SF-36 questionnaires. There was also a strong correlation between these questionnaires.

It is well known and documented that patients with cancer go through great physical and psychosocial stress since diagnosis, causing a variety of signs and symptoms that may last for some time after treatment^(3,7,44-47) even when results of treatment are positive^(3,28). Patients submitted to HSCT have an extra dose of factors that contribute even more to disability, such as conditioning regimens, restrictions before, during and after treatment and complications inherent to the procedure (including acute and chronic GVHD) that can occur in the early and late periods after the procedure.

Physical domain functions are considered predictors of longevity and good health and their parameters are being used in clinical trials as primary or secondary endpoints associated to clinical evaluation^(16,17). The instruments used in this study were chosen with the main objective of using one tool for each physical domain with simple and effective evaluations that can be performed in clinical settings.

The results of comparing physical parameters between the allogeneic and autologous groups in the Phase 1 evaluation were not statistically different, showing that the functional status of allogeneic and autologous patients are similar. Differences were observed for clinical parameters at Phase 2. Thus, an important limitation of our study was that our sample was not large enough to compare the Phase 2 results between the two groups. The different types of procedure may impact on function differently, but the analyses were not possible due to the small number of patients. Further investigations should be considered with larger sample sizes as some of the findings of this study may be confirmed or reinforced.

This study only verified physical impairment but it is known that psychic conditions might influence the physical performance and these variables should be investigated in future studies.

Conclusion

Significant differences identify decreases in aerobic conditioning before and after physical stress, declines in functioning and gait performance, reduction of muscle strength and spine flexibility and diminished functioning in daily activities after HSCT. The intensity and specificity may guide preventive measures and conduct a better rehabilitation program in the post-HSCT period.

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