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Assessment of pre-treatment cognitive performance in adult bone marrow or haematopoietic stem cell transplantation patients: A comparative study

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Abstract

The aim of this study was to examine cognitive performance in patients prior to bone marrow or haematopoietic stem cell transplantation (SCT) and in haematological patients who received non-myeloablative cancer therapies. A consecutive sample of 101 SCT patients and 82 haematological patients completed a neuropsychological test battery and five questionnaires assessing subjective cognitive complaints, psychological functioning, health-related quality of life and fatigue. Results were compared with normative data. Percentages of cognitively impaired patients were equally divided between groups. Most deficits were observed in visual memory, visuospatial and constructional ability and psychomotor functions. The SCT group showed a higher rate of anxiety cases and reported lower cognitive, emotional and social functioning. Results of neuropschychological testing were not associated with outcome of the questionnaires. This study showed impaired cognitive performance prior to SCT. Haematological patients treated with non-myeloablative cancer therapies proved to be a reliable reference group for longitudinal studies.

Keywords: Bone marrow transplantation; Haematological malignancies; Neuropsychological evaluation; Quality of life; Psychological functioning; Fatigue

1. Introduction

With more effective anticancer treatment, late side-effects of treatment are an increasing source of concern. This also holds for cognitive dysfunction. The most consistent cognitive deficits in patients treated for advanced malignancies outside the central nervous system (CNS) involve executive function, verbal memory and motor skills [1]. Even though most of these cognitive changes are mild or subtle, they can affect many aspects of patients' lives and have serious consequences for health-related quality of life (HRQOL), family role functions and employment status or vocational training.

Bone marrow or haematopoietic stem cell transplantation (SCT) in adults with haematological malignancies is a potential cause of cognitive dysfunction [2–12]. SCT patients are exposed to a variety of profound neurotoxic influences over a prolonged period. Firstly, most patients have faced intensive treatment schedules, such as high-dose systemic chemotherapy, intrathecal chemotherapy or relapse therapies, before undergoing SCT [13,14]. This

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is followed by the induction phase of SCT, which involves high-dose myeloablative chemotherapy with or without total body irradiation (TBI) [15]. Finally, post-engraftment, many patients need long-term immunosuppression with steroids or cyclosporin, they are at risk of opportunistic infections caused by immunosuppression and they experience acute or chronic graft versus host disease (GVHD) [16]. All these factors put SCT patients at an increased risk of CNS damage and result in possible long-term cognitive deficits. In a retrospective study of cognitive functioning in adult survivors of SCT, we observed that a significant proportion of patients experienced ongoing cognitive problems several years after SCT treatment [11].

The curative intent of SCT underscores the importance of evaluating long-term cognitive performance in these patients. Better insight and understanding of the cognitive consequences of SCT can be obtained by using a longitudinal repeated measurement design with a pre-SCT assessment. A pre-treatment measurement is of pivotal importance because it allows for differentiating between observed deficits due to the SCT procedure, the ensuing treatment and complications on the one hand, and deficits induced by the disease itself, pre-SCT treatment or confounding factors, such as psychological distress, on the other hand. Previous prospective reports showed cognitive deficits prior to SCT treatment in up to 60% of patients [4,5,12]. Although most of these studies used measures of psychological functioning, all failed to incorporate an appropriate reference group, which is necessary to draw conclusions about the underlying causes of the observed effects. However, there are inherent difficulties in selecting a reference group. Differences in pre-SCT treatment schedules, in particular in the intensity of chemotherapy, may cause varying degrees of cognitive deficits prior to SCT. In the present study, we therefore assessed cognitive performance, psychological functioning, fatigue and HRQOL in SCT patients prior to SCT and in a group of patients with haematological malignancies who were treated with systemic chemotherapy and/or involved-field radiotherapy. The objectives were to study pre-SCT cognitive functioning in a sufficiently large sample of SCT patients and its relation to potential confounding factors, and to investigate whether a group of patients with haematological malignancies treated with non-myeloablative cancer therapies can be used as a clinically relevant reference group in future longitudinal studies.

2. Patients and methods

2.1. Patient accrual and study procedure

SCT study participants and patients for the reference group were recruited from the outpatient clinics of the Departments of Haematology and Radiotherapy of the Erasmus Medical Center, Rotterdam ($n = 169$) and the Department of Haematology of Leiden University Medical Center in The Netherlands ($n = 14$). Inclusion criteria were: completion of (pre-SCT) treatment for a haematological malignancy, age 16–65 years and fluent in Dutch. Patients were excluded in cases of previous or current neurological or psychiatric disorders with known impact on cognitive and/or motor functions, and in cases of previous or current substance abuse. Patient accrual began in June 1999 and lasted until December 2001. All patients were asked by their doctor to take part in the study. An appointment for assessment of the patient was scheduled before starting SCT induction regimens. The institutional ethics committee for each participating centre approved the research protocol and all patients provided written informed consent. Medical data were collected from the patients' records. Performance status was assessed using the Karnofsky performance status scale (KPS) [17].

2.2. Assessment of cognitive performance

A comprehensive test-battery was designed to assess four cognitive domains: *Memory and learning:* the Dutch version of the California verbal learning test [18], the Rey complex figure test and recognition trial [19], the Benton visual retention test [20]; *Attention and executive functions:* Category wordfluency [21]; Digit span [22], the abbreviated Stroop colour-word test [23,24], Trails A and B [25], the D2 test [26]; *Visuospatial and constructional ability:* the Rey complex figure test-copy trial [19], Block design [22]; *Psychomotor functions:* Digit symbol [22], Finger tapping [27]; the Reaction time test [28]. In addition, the Dutch version of the National Adult Reading test [29] was used to estimate pre-morbid intelligence level. All tests were selected with regard to available normative data and their sensitivity to measure specific cognitive deficits. The tests were administered in the same order to each patient and the assessment took approximately 2 h to complete.

2.3. Assessment of subjective cognitive functioning

The Dutch version of the Cognitive Failure Questionnaire (CFQ) was administered to measure the frequency of everyday cognitive failures in memory, attention, action and perception [30]. It has 25 items with a 5-point scale from 0 (never) to 4 (very often). Raw scores were transformed and a total CFQ-score was computed by summing the item scores. The total CFQ scores range from 0 to 100, with higher scores indicating more cognitive failures. Additionally, all patients (except for those who reported no cognitive failures) indicated if they experienced an increase in cognitive failures in the last

year, if they were hindered, worried and annoyed about the cognitive failures.

2.4. Assessment of psychosocial functioning, fatigue and HRQOL

The Hospital Anxiety and Depression Scale (HADS), comprising 14 items, was used to screen for anxiety and depression [31]. A cut-off level of >10 points for both subscales was used to identify potential clinical cases [32]. The severity of psychological reactions to disease and treatment was evaluated with the Impact of Event Scale (IES) [33]. The IES relates to specific events associated with stress disorders and is based on a list of comments composed of commonly reported experience of intrusion (7 items) and avoidance (8 items). Patients have to indicate how frequently these comments applied to them during the past week on a 4-point scale with scores ranging from 0 (not at all) to 5 (often). Separate scores of intrusion of disease, intrusion of treatment, avoidance of disease and avoidance of treatment were computed, ranging from 0 to 35 for the intrusion scales and from 0 to 40 for the avoidance scales, with higher scores indicating more complaints.

The Multi-dimensional Fatigue Inventory (MFI) was used to measure fatigue [34]. The MFI has five subscales assessing general fatigue, physical fatigue, mental fatigue, reduced activity and reduced motivation. The subscale scores range from 4 to 20 with higher scores representing more symptoms.

HRQOL was measured with the EORTC QLQ-C30 [35]. This instrument incorporates functional and symptom scales, symptom items and two scales to assess health and global QOL. All scores were transformed ranging from 0 to 100 [36]. The Leukaemia-BMT module (QLQ-LEU-BMT) was added to evaluate somatic symptoms associated with SCT [37].

2.5. Data analyses

The neuropsychological test scores were compared with normative data adjusted for age and gender. Raw test scores were converted into standard (z-scores) scores. Patients were classified as cognitively impaired when scores were more than 1.5 standard deviation (SD) below the mean of the standard scores on at least 4 sub-tests [27]. A measure of overall cognitive performance was derived for each individual patient by summing the number of impaired test scores divided by the number of completed tests and multiplied by 100. Descriptive statistics were used to summarise the demographic and clinical characteristics, neuropsychological test scores and questionnaires responses. Because of a large number of categorical potential confounding variables, a multivariate confounder score (using gender, diagnosis, relapse, chemotherapy and radiotherapy) was calculated for each patient to reduce a bias in test results [38]. Differences between groups in raw neuropsychological test scores and the scores of the questionnaires were tested by univariate analysis of covariance (ANCOVA) with the multivariate confounder score as a co-variate. Between-group differences in other variables were evaluated using Student's t-tests for independent samples (two-sided) or χ^2 tests. Pearson's correlation coefficients were calculated to assess the relations between various variables, test scores and measure of overall cognitive performance. A 0.05 level of statistical significance was used in all statistical procedures. Analyses were performed using the Statistical Package for the Social Sciences (SPSS) Windows 11.0 software.

3. Results

3.1. Patients characteristics

Of the 151 patients scheduled for SCT, 135 (89%) met the inclusion criteria. In the reference group, 99 (83%) of the 119 consecutive patients were eligible for study. The main reasons for exclusion in both groups were: age over 65 years, language difficulties and concomitant neurological disorders. Thirty-three (24%) SCT patients and 17 (17%) patients in the reference group refused to participate. The primary reported reason for refusal in the SCT group was the burden of an additional assessment along with many other medical examinations before long-term hospitalisation for SCT. In the reference group the main reported reason for refusal was that patients wished not to be confronted with their disease after the end of treatment. One SCT patient was unable to complete the assessment and was excluded from the study. All remaining 101 SCT patients completed the pre-treatment assessment prior to the start of the SCT induction phase. The mean time between the assessment and the start of SCT treatment was 21 d (SD = 23.0). Thirty-five (34%) SCT patients were scheduled for autologous SCT, 42 (42%) for an allogeneic related-donor transplant and 24 (24%) for an unrelated-donor transplant. The patients' characteristics are described in Table 1. Gender was not equally distributed ($P = 0.03$) when comparing both groups.

Two SCT patients received no treatment prior to transplant. All other patients (98%) received chemotherapy according to standard treatment protocols and 19 (19%) had additional (non-cranial) radiotherapy. In the reference group, chemotherapy had been given to 74 (90%) patients. Radiotherapy (mantle field and mediastinal fields) subsequent to chemotherapy was administered to 52 (63%) patients. Eight (10%) patients in the reference group received radiotherapy as primary treatment. Intrathecal chemotherapy was given to 11 (11%) SCT patients as opposed to 1

Table 1
Demographic and clinical patients characteristics

Characteristics	SCT group ($n = 101$)	Reference group ($n = 82$)	P-value
Gender, n (%)			0.02
Male	62 (61)	37 (45)	
Female	39 (39)	45 (55)	
Age (years), mean (SD)	42.0 (12.1)	39.2 (13.1)	0.14
Pre-morbid IQ, mean (SD)[a]	104.6 (10.7)	102.9 (10.7)	0.28
KPS, mean (SD)[b]	83.7 (8.4)	85.2 (8.4)	0.20
Educational level, n (%)			0.90
Less than high school	5 (5)	4 (5)	
High school	30 (30)	24 (29)	
Vocational/trade school	37 (36)	31 (38)	
College/bachelor degree	19 (19)	18 (22)	
University degree	10 (10)	5 (6)	
Civil status, n (%)			0.70
Married/living with partner	77 (76)	59 (72)	
Single, divorced, widowed	24 (24)	23 (28)	
Pre-morbid employment status, n (%)			0.78
Full-time work	51 (50)	43 (52)	
Part-time work	25 (25)	21 (26)	
Housewife or student	18 (18)	12 (14)	
Disability benefits	1 (1)	3 (4)	
Pension	6 (6)	3 (4)	
Current employment status, n (%)			0.51
Full-time work	2 (2)	5 (6)	
Part-time work	6 (6)	8 (10)	
Housewife or student	18 (18)	14 (17)	
Disability benefits	16 (16)	7 (8)	
Pension	7 (7)	4 (5)	
Sick-leave	52 (51)	44 (54)	
Primary diagnosis, n (%)			<0.001
Acute myelogenous leukaemia	19 (19)	1 (1)	
Acute lymphocytic leukaemia	8 (8)	0	
Chronic myelogenous leukaemia	16 (16)	1 (1)	
Chronic lymphocytic leukaemia	1 (1)	1 (1)	
Non-Hodgkin's lymphoma	30 (29)	28 (34)	
Hodgkin's disease	4 (4)	49 (60)	
Multiple myeloma	17 (17)	2 (3)	
Myelodysplastic syndrome	3 (3)	0	
Other[c]	3 (3)	0	
Relapse, n (%)			<0.001
No	58 (57)	74 (90)	
Yes, first relapse	30 (30)	6 (7)	
Yes, >1 relapse	13 (13)	2 (3)	
Chemotherapy, n (%)			<0.001
No previous chemotherapy	2 (2)	8 (10)	
1 course of chemotherapy	47 (47)	71 (86)	
>1 course of chemotherapy	52 (51)	3 (4)	
Intrathecal chemotherapy, n (%)			0.007
Yes	11 (11)	1 (1)	
No	90 (89)	81 (99)	
Radiotherapy (non-CNS), n (%)			<0.001
Yes	19 (19)	60 (73)	
No	82 (81)	22 (27)	
Time since diagnosis (years), mean (SD)	1.6 (2.9)	1.1 (2.1)	0.16
Time since treatment (months), mean (SD)	2.7 (4.0)	2.0 (2.1)	0.15

SCT, bone marrow or haematopoietic stem cell transplantation; CNS, central nervous system; SD, standard deviation.
[a] Derived from the Dutch National Adult Reading Test.
[b] KPS = Karnofsky Performance Score.
[c] Other = aplastic anaemia, amyloidosis, Waldenstrom's macroglobulinaemia.

(1%) patient in the reference group ($P = 0.01$). Forty-three percent of SCT patients had been treated for a relapse, in contrast to 10% in the reference group ($P < 0.001$). There was no between-group difference in time interval between last treatment and the neuropsychological assessment.

3.2. Cognitive performance

Comparisons of the assessment prior to SCT showed minor group differences on neuropsychological tests (Table 2). The SCT group was slower on the Trails A than the reference group ($P = 0.03$). No differences between groups were found in percentages of impaired patients (compared with normative data). Most deficits were seen in visual memory, visuospatial and constructional ability and psychomotor functions. The measure of overall cognitive performance was not significantly different between groups (9.2 in the SCT group and 8.3 in the reference group, respectively; $P = 0.47$). No differences were observed between groups in the percentages of impaired test scores per cognitive domain. Twelve percent of the SCT patients and 8.5% of the patients in the reference group had impaired scores on more than 20% (i.e., >5 of the 26 subtests) of the neuropsychological tests. No associations were found between cognitive performance and treatment parameters.

3.3. Subjective cognitive functioning

Results of the CFQ are shown in Table 3. Comparisons of the mean CFQ scores with published norms indicated that total scores fell within normal limits (i.e., very

Table 2
Neuropsychological results: raw means ± SD by group (adjusted means[a]) and percentage of impaired patients

	SCT group ($n = 101$)	Reference group ($n = 82$)	P-value[b]
Memory and learning			
Verbal learning			
CVLT, total score list A	54.3 ± 9.9 (53.9) 8%	54.7 ± 9.9 (55.3) 11%	0.46
Verbal memory			
CVLT, short-delay free recall	11.4 ± 2.6 (11.6) 11%	11.9 ± 2.6 (11.7) 14%	0.91
CVLT, consolidation	2.0 ± 2.8 (12.1) 8%	12.2 ± 2.6 (12.1) 10%	0.10
CVLT, recognition	14.9 ± 1.4 (15.0) 8%	15.1 ± 1.1 (15.0) 4%	0.10
CVLT, false-positives	0.9 ± 1.6 (0.9) 0%	0.9 ± 1.4 (0.9) 0%	0.91
Visual memory			
RCFT, short-delay recall	20.9 ± 6.2 (21.1) 15%	21.9 ± 5.9 (21.7) 13%	0.58
RCFT, long-delay recall	20.9 ± 6.3 (21.2) 18%	22.1 ± 5.7 (21.8) 15%	0.63
RCFT, recognition	20.2 ± 2.0 (20.2) 17%	20.5 ± 2.1 (20.5) 16%	0.42
BVRT, no. correct	7.4 ± 1.7 (7.4) 2%	7.6 ± 1.6 (7.6) 1%	0.52
BVRT, no. wrong	3.5 ± 2.7 (3.6) 11%	3.2 ± 2.4 (3.2) 5%	0.44
Attention and executive functions			
Category wordfluency	20.5 ± 4.5 (20.3) 1%	20.5 ± 4.1 (20.7) 0%	0.68
Digit span, total score	12.9 ± 3.6 (12.8) 1%	13.0 ± 3.3 (13.1) 1%	0.65
Stroop colour-word card, total time	90.8 ± 35.9 (89.0) 11%	89.7 ± 19.8 (91.9) 13%	0.61
Trails A, total time	33.8 ± 13.9 (35.0) 4%	30.9 ± 11.7 (29.4) 2%	0.03
Trails B, total time	72.2 ± 28.3 (71.9) 1%	66.4 ± 27.4 (66.8) 2%	0.35
D2 test, total score GZ	409.6 ± 76.8 (405.6) 3%	417.8 ± 77.9 (422.7) 2%	0.25
D2 test, total score F%	4.2 ± 3.7 (4.4) 0%	4.3 ± 3.2 (4.1) 0%	0.57
D2 test, total score KL	155.1 ± 34.4 (152.2) 10%	161.7 ± 40.8 (165.2) 10%	0.07
Visuospatial and constructional ability			
RCFT, total score copy	34.0 ± 2.9 (34.0) 20%	34.4 ± 1.9 (34.3) 16%	0.59
Block design, total score	18.8 ± 6.2 (18.9) 0%	19.7 ± 5.6 (19.3) 0%	0.57
Psychomotor functions			
Digit symbol, total score	54.2 ± 11.3 (54.3) 1%	56.7 ± 10.8 (56.6) 0%	0.29
FT, total score dominant hand	353.6 ± 51.1 (352.0) 13%	352.9 ± 46.3 (354.8) 16%	0.76
FT, total score non-dominant hand	305.6 ± 51.7 (305.6) 21%	302.9 ± 49.7 (302.9) 18%	0.78
RTT, decision time single stimuli	322.8 ± 39.1 (323.9) 6%	320.3 ± 42.1 (319.0) 7%	0.54
RTT, motor time single stimuli	146.5 ± 41.2 (150.8) 16%	144.3 ± 39.9 (139.2) 10%	0.15
RTT, decision time complex stimuli	515.4 ± 82.0 (515.8) 17%	509.5 ± 94.5 (509.0) 22%	0.70
RTT, motor time complex stimuli	150.1 ± 50.8 (152.2) 20%	148.2 ± 44.7 (145.7) 12%	0.49
RTT, error score	1.7 ± 2.4 (1.9) 11%	1.4 ± 1.5 (1.2) 7%	0.08

Percentage of impaired patients in *italics*.
SCT, bone marrow or haematopoietic stem cell transplantation; CVLT, California verbal learning test; RCFT, Rey complex figure test and recognition trial; BVRT, Benton visual retention test; GZ, total number of identified targets; F%, percentage of errors and omissions; KL, accuracy score; FT, Finger tapping; RTT, Reaction time test.
[a] Raw mean test scores adjusted for confounding factors.
[b] Adjusted P-values.

Table 3
Subjective cognitive complaints: mean scores ± SD (adjusted means[a]) of the Cognitive Failure Questionnaire

	SCT group ($n = 101$)	Reference group ($n = 82$)	P-value
CFQ			
Total score[b]	26.2 ± 12.6 (26.6)	28.0 ± 14.1 (27.6)	0.69[b]
CFQ score-distribution[c], n (%)			0.13
Very low score	14 (14)		9 (11)
Low score	20 (20)		19 (23)
Average score	57 (56)		36 (44)
High score	7 (7)		15 (18)
Very high score	3 (3)		3 (4)
Increase in cognitive failures[d]			0.46
No increase	49 (51)		31 (40)
Little increase	31 (32)		33 (42)
Moderate increase	11 (12)		9 (12)
Quite an increase	4 (4)		5 (6)
Very strong increase	1 (1)		0
Hindered by cognitive failures[d]			0.30
No hindrance	33 (34)		23 (30)
Little hindrance	41 (43)		30 (38)
Moderate hindrance	20 (21)		19 (24)
Quite some hindrance	2 (2)		6 (8)
Very much hindrance	0		0
Worried by cognitive failures[d]			0.39
No worries	55 (57)		38 (49)
Little worries	26 (27)		20 (26)
Moderate worries	13 (14)		16 (20)
Quite a lot worries	2 (2)		4 (5)
Very much worries	0		0
Annoyed about cognitive failures[d]			0.15
No annoyance	42 (44)		31 (40)
Little annoyance	41 (43)		25 (32)
Moderate annoyance	8 (8)		14 (18)
Quite a lot annoyance	5 (5)		7 (9)
Very much annoyance	0		1 (1)

SCT, bone marrow or haematopoietic stem cell transplantation; CFQ, Cognitive Failure Questionnaire.
[a] Mean scores adjusted for confounding factors.
[b] $P = 0.69$ (adjusted P-value of an ANCOVA).
[c] CFQ scores compared with normative data.
[d] 96 SCT patients and 78 control patients completed these additional questions.

low, low or average score) for the majority of SCT patients and the reference group (respectively, 90% and 78%). There was no difference in the total score between groups. The percentages of patients reporting an increase in cognitive failures or who were hindered, worried or annoyed about their cognitive failures were small. The distributions of these scores were not different between groups.

3.4. Psychological functioning, fatigue and HRQOL

Table 4 shows the results of the questionnaires of psychological functioning and fatigue. No differences in mean scores of anxiety and depression of the HADS were found between groups. The number of anxiety cases (i.e., scale score > 10) was higher in the SCT group, but no differences were found in the number of depression cases between groups. In both groups, no correlations were observed between the HADS and cognitive performance. No differences between groups were found in mean subscale scores of the IES and the MFI. The scores of the IES and the MFI were not associated with cognitive performance.

Analysis of the EORTC QLQ-C30 and the QLQ-LEU-BMT revealed that the SCT patients had lower scores (i.e., lower level of functioning) on cognitive, emotional and social functioning compared with the patients in the reference group (Table 5). Higher scores (i.e., more complaints) for the reference group were found on the symptom item dyspnoea. On the QLQ-LEU-BMT, the SCT patients reported higher scores on chills, fever, weight loss, mouth sores and functional status. The HRQOL scores were not related to cognitive performance.

4. Discussion

This comparative study constitutes the largest published sample of SCT patients evaluated with a

Table 4
Psychological functioning: means ± SD (adjusted means) of the Hospital Anxiety and Depression Scale, the Impact of Event Scale, and the Multi-Dimensional Fatigue Inventory

	SCT group (n = 101)	Reference group (n = 82)	P-value[b]
HADS[a]			
Anxiety	5.5 ± 4.0 (5.5)	4.7 ± 3.5 (4.7)	0.30
Depression	3.7 ± 3.4 (3.6)	3.7 ± 3.5 (3.8)	0.77
Anxiety >10, n (%)	14 (13.9)	3 (3.7)	0.02
Depression >10, n (%)	5 (5.0)	7 (8.5)	0.34
IES[a]			
Intrusion disease	11.0 ± 7.5 (10.9)	9.4 ± 6.7 (9.5)	0.90
Intrusion treatment	7.8 ± 6.9 (8.3)	8.5 ± 6.7 (7.9)	0.79
Avoidance disease	10.6 ± 8.9 (10.5)	7.4 ± 7.3 (7.5)	0.06
Avoidance treatment	8.3 ± 8.4 (8.8)	6.7 ± 7.3 (6.0)	0.06
MFI[a]			
General fatigue	11.0 ± 4.7 (11.1)	12.1 ± 4.4 (12.0)	0.34
Physical fatigue	11.2 ± 5.0 (11.3)	12.2 ± 5.1 (12.0)	0.48
Reduced activity	10.5 ± 5.0 (10.6)	11.1 ± 5.0 (11.0)	0.71
Reduced motivation	8.0 ± 3.9 (7.6)	8.4 ± 4.1 (8.8)	0.14
Mental fatigue	9.6 ± 4.6 (9.7)	9.8 ± 4.3 (9.7)	0.94

SCT, bone marrow or haematopoietic stem cell transplantation; HADS, Hospital anxiety and depression scale; IES, impact of event scale; MFI, multi-dimensional fatigue inventory.
[a] Mean scores adjusted for confounding factors.
[b] Adjusted P-values.

comprehensive battery of neuropsychological tests prior to SCT treatment and is the first to compare the results with a reference group of haematological patients. It revealed that up to approximately 20% of SCT patients showed deficits in visual memory, visuospatial and constructional ability, and psychomotor functions before undergoing SCT treatment. No significant correlation was found between patients' subjective estimations of cognitive performance in daily-life functioning and the results of objective neuropsychological testing.

These findings are in line with three other reports, despite differences in design and methods [4,5,12]. Andrykowski and colleagues [4] found cognitive impairment in 56% of 55 SCT candidates. Meyers and colleagues [5] observed cognitive dysfunction in 20% of 61 SCT candidates by using a self-reporting instrument to identify cognitive problems. Recently, Sostak and colleagues [12] found abnormal results in a neuropsychological examination in 58% of 71 allogeneic SCT patients.

To date, research has centred on cognitive functions in SCT patients only. By using a reference group, we were able to examine differences in cognitive functioning prior to SCT between SCT candidates and haematological patients treated with chemotherapy, radiotherapy, or a combination of these. The results showed no between-group differences in degree or patterns of cognitive impairment. Patients in the reference group scored slightly higher in only 1 out of 26 neuropsychological subtests. Using a different threshold for statistical significance ($P = 0.01$) to correct for multiple testing would not have altered our findings. In both groups correlation between cognitive performance and specific treatment parameters was lacking. Therefore, it is possible that the observed cognitive dysfunctions in our patients might be attributed to the treatment they have undergone (i.e., chemotherapy, radiotherapy and adjuvant drugs), the underlying disease or a combination of these factors.

Between 90% and 98% of all patients in our study were treated with at least one course of systemic chemotherapy at an average time interval of 2–3 months before the neuropsychological assessment. Most cytotoxic agents, although some more than others, are known to affect both the CNS and the peripheral nerves [39]. A variety of treatment induced neurological complications have been described, including peripheral neuropathies, leucoencephalopathies and cerebellar symptoms [40]. In some instances, these complications are persistent and involve structural changes in the brain, in particular white matter lesions (mainly in the subcortical areas), brain atrophy and ventricular dilation.

Support for the hypothesis that systemic chemotherapy has a negative impact on cognitive functioning comes from research comparing systemic chemotherapy with local therapy (i.e., surgery and local radiotherapy) in breast cancer and lymphoma patients [41]. Patients in chemotherapy groups showed more cognitive impairment compared with those treated with local therapy only. In contrast, we observed no significant differences between patients treated with systemic chemotherapy or local radiotherapy only. Furthermore, there was an absence of significant

Table 5
EORTC QOL questionnaire and Leukemia-BMT module: means ± SD (adjusted means[a])

	SCT group (n = 101)	Reference group (n = 82)	P-value[b]
QLQ-C30 functioning scales[c]			
Physical functioning	74.3 ± 23.2 (74.4)	77.1 ± 19.7 (77.1)	0.53
Role functioning	62.4 ± 31.1 (61.6)	69.5 ± 26.2 (70.4)	0.12
Cognitive functioning	76.5 ± 10.0 (75.0)	83.5 ± 17.6 (83.6)	0.02
Emotional functioning	70.2 ± 28.3 (68.9)	79.4 ± 18.8 (81.4)	0.009
Social functioning	69.2 ± 29.8 (68.0)	76.8 ± 23.4 (78.3)	0.05
Global health	66.7 ± 23.0 (65.5)	66.5 ± 18.8 (67.8)	0.58
Global quality of life	71.0 ± 21.5 (70.6)	72.4 ± 21.2 (72.9)	0.58
QLQ-C30 symptom scales and items[d]			
Fatigue	31.9 ± 25.5 (34.4)	38.3 ± 25.4 (35.4)	0.82
Nausea/vomiting	5.1 ± 13.1 (5.0)	7.3 ± 16.2 (7.5)	0.39
Pain	16.8 ± 25.2 (18.7)	13.8 ± 20.3 (11.5)	0.10
Dyspnoea	15.3 ± 20.8 (13.0)	21.9 ± 25.8 (24.8)	0.009
Sleep disturbances	20.7 ± 28.3 (23.3)	19.9 ± 28.1 (16.8)	0.23
Appetite loss	7.0 ± 17.3 (7.5)	9.3 ± 19.1 (8.8)	0.71
Constipation	4.7 ± 14.3 (4.5)	3.3 ± 10.0 (3.5)	0.69
Diarrhoea	10.4 ± 18.8 (8.3)	5.7 ± 15.5 (8.3)	1.0
Financial impact	14.5 ± 25.7 (14.4)	9.8 ± 20.6 (9.8)	0.31
QLQ-LEU-BMT symptom scales and items[d]			
Chills	17.5 ± 24.0 (18.1)	9.9 ± 17.0 (9.1)	0.03
Itchy skin	22.3 ± 30.7 (20.5)	20.6 ± 30.7 (23.0)	0.65
Dry skin	29.7 ± 28.4 (29.0)	28.4 ± 25.9 (29.5)	0.93
Stiff joints	24.9 ± 27.0 (21.9)	20.2 ± 24.0 (22.6)	0.89
Feeling cold	24.0 ± 26.8 (25.3)	21.4 ± 28.5 (20.2)	0.34
Flushes	10.4 ± 20.0 (9.6)	10.7 ± 21.6 (11.8)	0.59
Headache	12.8 ± 19.5 (13.5)	13.2 ± 19.5 (12.3)	0.76
Hearing loss	6.1 ± 18.7 (6.3)	3.3 ± 10.0 (3.0)	0.26
Pain during sex	7.1 ± 17.4 (7.8)	6.2 ± 16.8 (5.3)	0.44
Fever	15.2 ± 25.8 (16.1)	4.9 ± 13.0 (3.8)	0.003
Infection	15.5 ± 24.9 (16.2)	9.5 ± 18.4 (8.6)	0.08
Weight loss	10.4 ± 19.4 (12.4)	6.6 ± 17.0 (4.2)	0.02
Abdominal pain	11.5 ± 21.9 (12.1)	12.8 ± 20.1 (12.0)	0.98
Mouth sores	11.8 ± 23.5 (12.4)	3.3 ± 12.5 (2.5)	0.009
Pain during urination	1.0 ± 5.7 (1.7)	2.1 ± 8.1 (1.2)	0.73
Blood in urine	1.3 ± 8.1 (1.5)	.4 ± 3.7 (.3)	0.36
ensory loss	18.0 ± 22.5 (17.9)	13.2 ± 19.7 (13.3)	0.26
Functional status	4.4 ± 12.0 (4.7)	.6 ± 3.2 (.2)	0.01

SCT, bone marrow or haematopoietic stem cell transplantation; QLQ-C30, EORTC QOL questionnaire, QLQ-LEU-BMT, Leukemia-BMT module.
[a] Mean scores adjusted for confounding factors.
[b] Adjusted P-values.
[c] Scores on functioning scales range from 0 to 100 with a higher score indicating better functioning.
[d] Scores on the symptoms scales and items range from 0 to 100 with higher scores meaning more bothered by complaints.

differences between patients treated with one course of chemotherapy or those who received multiple courses. The similarities of the cognitive dysfunctions found in our patient groups suggest that differences in treatment intensity between groups play no prevailing role in the development of cognitive impairment. Thus, it is unlikely that chemotherapy-related neurotoxicity is the only cause of the observed cognitive deficits in our patient population.

Besides chemotherapy, other factors could be involved in the aetiology of cancer-related cognitive impairment. Systemic chemotherapy is often given in combination with adjuvant drugs (e.g., corticosteroids) or other treatment modalities. High doses of exogenous corticosteroids might well affect CNS structure and functioning. Reduced hippocampal volume and memory deficits in patients receiving chronic corticosteroid therapy have been reported previously [42]. Similarly, synergistic effects of combined treatment have been noted to play a role in impaired cognitive functioning of primary CNS lymphoma patients [43]. Lastly, cytokines released from the tumour tissue or exogenous cytokines used in immunotherapy (e.g., interferon-α), could affect CNS functioning and have a sizeable effect on cognitive performance [44]. Further research into the identification of specific cytotoxic agents, combined effects of drugs and other additional factors responsible for CNS damage is required and should increase the understanding

of the specific mechanisms involved in the development of cognitive deficits after cancer treatment.

This assessment of psychological functioning, HRQOL and fatigue prior to SCT confirms earlier findings that anxiety, depression, sleep disturbances, or fatigue are common complaints in patients before undergoing SCT [4–6]. The number of anxiety cases in our sample of SCT patients was indeed substantially higher than in the reference group and we also observed distinct differences between the two groups on a number of HRQOL functioning scales and symptom items. The between-group differences in the symptom items suggest a relationship with adverse effects of previous treatment, either radiotherapy with mantle and mediastinal fields or pre-SCT chemotherapy schedules. Of particular importance is the finding that none of the between-group differences in psychological functioning or HRQOL affected cognitive performance. A contributing effect of psychological distress, related to either the disease itself or its treatment, on cognitive performance in our patient groups, is probably not significant.

The present findings indicate that doctors or healthcare practitioners preparing patients for the transplantation and its complications should be aware of a wide range of cognitive and emotional problems associated with treatment prior to SCT. More importantly, they should be sensitive to further functional declines in these particular areas. For the moment, greater effort should be directed to translate the outcome of the assessments into the development of educational interventions and perhaps cognitive rehabilitation programs. Preventive rehabilitation programs, in particular, could minimise further functional loss, facilitate recovery after SCT treatment, and thereby retard the patient's loss of well-being and enhance HRQOL.

In conclusion, this study has provided additional information about pre-transplant cognitive performance in SCT patients and its relation to confounding factors, in part by being the first to specifically evaluate this in comparison to a reference group. The results confirm that cognitive performance is impaired prior to SCT treatment. Also, they showed that cognitive impairment is not associated with confounding psychological factors, nor that it is different to patients treated with conventional cancer therapies. More research is needed to identify whether these observed effects are reversible or persist over time, and to investigate whether SCT patients develop further deterioration after additional SCT treatment. A longitudinal study in SCT patients is now being undertaken to explore these critical issues. Our data emphasise that prospective longitudinal designs using a similar reference group of patients with haematological malignancies are required for future trials on the cognitive impact of SCT.

Conflict of interest statement

None declared.

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