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Case-referent comparison of cognitive functions in patients receiving haematopoietic stem-cell transplantation for haematological malignancies: Two-year follow-up results

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ABSTRACT

During bone marrow or haematopoietic stem-cell transplantation (HSCT), potentially neurotoxic treatments are used. Previous studies identified cognitive disturbances in patients treated with HSCT, but prospective studies with longitudinal assessment are sparse. We examined cognitive functions up to 20 months after a first baseline assessment in 101 patients undergoing HSCT and in 82 reference patients with a haematological malignancy treated with non-myeloablative cancer therapies. Baseline findings revealed no between-group differences and demonstrated mild cognitive impairments in both groups. Follow-up analyses showed no significant changes over time, though poorer performance in attention and executive function, and psychomotor function was found in HSCT patients. Our results suggest limited HSCT-related cognitive dysfunctions. Additional follow-up is necessary to assess long-term effects.

1. Introduction

Bone marrow or haematopoietic stem-cell transplantation (HSCT) is widely used for various malignant haematological disorders. As a rule HSCT is preceded by high-dose cytotoxic treatment and it is often combined with total body irradiation (TBI) to eradicate the malignant disease and suppress the immune system to allow engraftment of donor or autologous stem-cells or bone marrow.[1] Complications related to HSCT treatment are generally due to toxicity associated with the myeloablative chemo-radiotherapy, to the period of profound immunodeficiency, and to graft-versus-host disease (GVHD).[2–4] Both high dose chemotherapy and radiotherapy to the brain have been related to delayed central nervous system (CNS) toxicity, in particular to delayed leuko-encephalopathy resulting in cognitive deficits.[5] As many HSCT associated complications

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are now better controlled, delayed central nervous system toxicity might become a clinically relevant long-term side-effect in HSCT treated patients. Cross-sectional retrospective studies demonstrated poor cognitive performance after HSCT.[6–10] Most longitudinal reports have focused on the period before, during and shortly after hospitalisation for HSCT.[11–14] Two prospective studies reported cognitive functions up to 14 months after allogeneic HSCT.[15,16] In both reports, serial formal neuropsychological testing was performed in over 50 patients using several standardised instruments covering memory, attention, executive and psychomotor functions. Sostak and colleagues found cognitive dysfunctions, in particular poorer performance in executive functions, in half of the patients evaluated before HSCT and at 14 months after transplant.[15] Risk factors for impairment included the presence of acute GVHD, prolonged immunosuppression, and metabolic disturbances. Syrjala and colleagues found a generalised cognitive decline at 80 days after HSCT, with recovery to pre-transplant levels at one year in most cognitive domains, except for motor dexterity and grip strength.[16] Here, chemotherapy prior to HSCT and treatment for GVHD were associated with cognitive impairment.

At present, there are no longitudinal data documenting cognitive changes following HSCT in comparison to a disease-specific reference group. Such a comparison is essential to specify which cognitive changes are related to disease and to previous treatment, and which are related to HSCT. In order to address this problem, we conducted a prospective longitudinal study to examine cognitive changes up to 20 months after baseline in adult patients undergoing HSCT for haematological malignancies in comparison to a disease-specific reference group that did not undergo HSCT. Baseline findings of this study were published previously in this journal and revealed no between-group differences.[17] Mild cognitive dysfunctions were found in both groups, predominantly in visual memory, visuospatial function and psychomotor function. In this article, we describe the follow-up results of our study.

2. Patients and methods

Serial neuropsychological assessments were carried out in a consecutive group of patients before undergoing HSCT (time 1 [T1]), and at intervals of 8 months (time 2 [T2]) and 20 months (time 3 [T3]) after baseline. Similar assessments were done in the disease-specific reference group (REF), mainly patients with Hodgkin's disease and lymphoma. Patients eligible for study were between 16 and 65 years of age, had completed (pre-transplant) treatment for a haematological malignancy or disorder, were fluent in Dutch, and were unfamiliar with psychopathology, neurological disorders or substance abuse.

A comprehensive battery of 13 neuropsychological standardised tests was designed to assess pre-morbid intelligence (National adult reading test[18]), verbal memory (California verbal learning test[19]), visual memory (Rey complex figure test and recognition trial,[20] Benton visual retention test[21]), attention and executive function (Category wordfluency,[22] WAIS Digit span,[23] Trailmaking A and B,[24] abbreviated Stroop color-word test,[25] D2-test[26]), visuospatial function (Rey complex figure test and recognition trial-copy trial,[20] WAIS Block design[23]), and psychomotor function (WAIS Digit symbol,[23] Finger tapping,[27] Reaction time test[28]). Test scores were compared to published normative data, and standard deviations from the normative mean were calculated for each test (mean = 0; standard deviation = 1.0) to facilitate comparisons among measures. Impairment on a test was defined as $\leqslant$2.0 standard deviations from the normative mean. Composite test scores were calculated for each cognitive domain and a measure of overall cognitive functioning was computed based on the number of impaired tests.

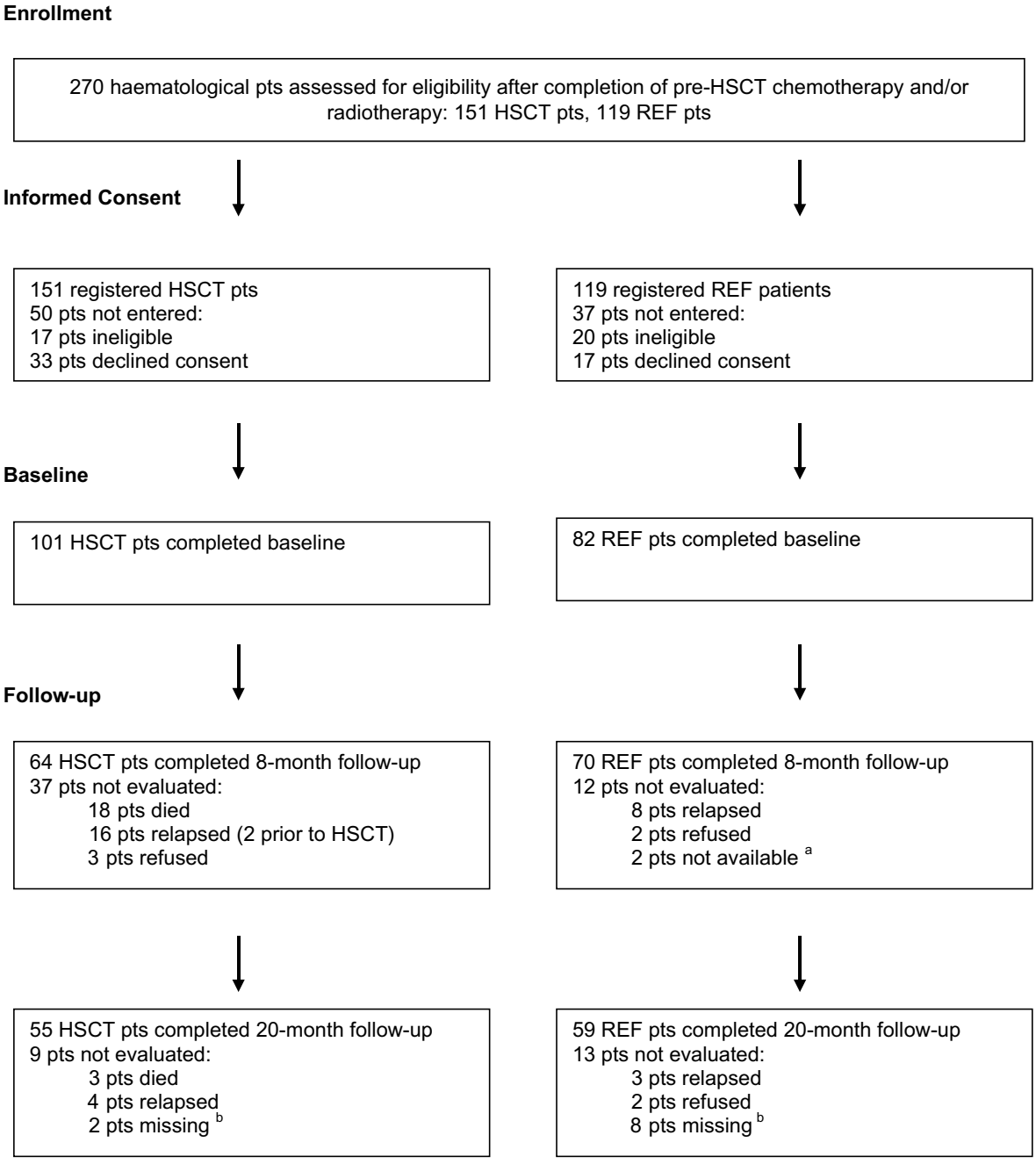
In addition to the neuropsychological tests, six questionnaires were used to measure subjective cognitive functioning (Cognitive failure questionnaire[29]), health related quality of life (HRQOL) (EORTC QLQ-C30,[30] MRC/EORTC QLQ Leukaemia-BMT module[31]), fatigue (Multi-dimensional fatigue inventory[32]), and general and cancer-related distress (Hospital anxiety and depression scale,[33,34] Impact of event scale[35]).

Data analyses involved the calculation of a multivariate confounder score (using gender, diagnosis, relapse and pre-transplant treatment) in order to reduce a potential bias in test results, due to a large number of categorical potential confounding demographical (i.e. gender) and clinical variables (i.e. diagnosis, relapse and pre-transplant treatment).[17,36] Between-group differences were evaluated using Student's *t*-tests for independent samples (two-sided) or X^2-analysis. Group differences in cognitive functions were tested by univariate analysis-of-covariance (ANCOVA) with the multivariate confounder score as a covariate. To determine changes in cognitive functions over time, random regression models (RRM) analyses were conducted for all cognitive domains.[37,38] The RRM approach allows for missing observations, time-varying covariables, invariant covariables and assessments at unequal end-points. RRM estimates both average time trends and individual time trends. The approach allows for modelling changes of variances in cognitive functions and changes in correlations between cognitive functions and covariables. Pearson's correlation techniques were used to evaluate associations between measures and treatment-related variables. The probability level for statistical significance was set at 0.05 (two-tailed). Analyses were performed using the SPSS (version 11.0) and PROC MIXED (SAS System, version 8.2).

3. Results

3.1. *Patients and treatment*

The flow of patients through the study is summarised in Fig. 1. Seventeen HSCT patients (11%) and 20 REF patients (18%) were ineligible due to age over 65, language difficulties, and concomitant neurological disorders. Thirty-three HSCT patients (22%) declined to participate because of the burden of an additional assessment before hospitalisation for HSCT. Seventeen REF patients (14%) did not participate, mainly as they did not want to be confronted with their disease after the end of treatment. In total, 101 HSCT patients and 82 REF patients completed the baseline assessment. Fifty-five HSCT patients (54%) and 59 REF patients (72%) were assessed at



HSCT, bone marrow or haematopoietic stem-cell transplantation. REF, reference group. pts, patients

[a] Two patients were not available for T2 (evaluated at T1 and T3 only) because of work commitments

[b] Ten patients could not be evaluated at T3 because of end of the study

Fig. 1 – Flow of patients through the study.

each time point. Attrition was primarily caused by death and recurrent disease.

Table 1 displays the diagnosis of all patients, and conditioning regimen and type of transplant for the HCST group. Prior to transplant, 99 HSCT patients (98%) were treated with chemotherapy according to standard treatment protocols, and 19 received subsequent (non-CNS) radiotherapy. Seventy-four REF patients (90%) received chemotherapy, followed by radiotherapy in 63%. The most common conditioning regimen involved high-dose cyclophosphamide followed by TBI (74%). GVHD ratios were considered for allogeneic HSCT survivors. Four patients (11%) developed acute grade 3–4 GVHD. Chronic GVHD was observed in 37 patients at T2 (41%) and 34 patients at T3 (27%), of which 9 (24%) and 4 (12%) respectively, had extensive disease. Most chronic GVHD patients (90%) received immunosuppressive medication.

Table 1 – Clinical patient characteristics

Characteristics	HSCT group, $n = 101$	REF group, $n = 82$
Gender, n (%)		
Male	62 (61)	37 (45)
Female	39 (39)	45 (55)
Age, years		
Mean (SD)	42.0 (12.1)	39.2 (13.1)
Diagnosis, n (%)		
Lymphoma	30 (29)	28 (35)
Hodgkin's disease	4 (4)	49 (60)
Acute leukaemia	27 (27)	1 (1)
Chronic leukaemia	17 (17)	2 (2)
Multiple myeloma	17 (17)	2 (2)
Myelodysplasia	3 (3)	0
Other [a]	3 (3)	0
HSCT conditioning regimen[b], *n* (%)		NA
Cyclophosphamide and TBI [c]	73 (74)	
Cyclophosphamide and busulphan	6 (6)	
BEAC [d]	10 (10)	
BEAM [e]	7 (7)	
Other [f]	3 (3)	
Type of transplant, *n* (%)		NA
Autologous	34 (34)	
Allogeneic related	41 (42)	
Allogeneic unrelated	24 (24)	

HSCT, bone marrow or haematopoietic stem-cell transplantation; REF, reference; SD, standard deviation; NA, not applicable; TBI, total body irradiation.

a Aplastic anaemia, Amyloidosis, Waldenstrom's macroglobulinemia.

b 2 HSCT patients died before transplant ($n = 99$).

c TBI dose: 5 Gy or 6 Gy daily for 2 days, or 9 Gy for 1 day.

d BEAC, Busulphan (300 mg/m^2 for 1 day, Etoposide 100 mg/m^2 twice per day for 4 days, Ara-C 100 mg/m^2 twice per day for 4 days, Cyclophosphamide 15 mg/kg per day for 4 days).

e BEAM, Busulphan (300 mg/m^2 for 1 day, Etoposide 125 mg/m^2 twice per day for 4 days, Ara-C 100 mg/m^2 twice per day for 4 days Melphalan 140 mg/ m^2 for 1 day).

f CBV , Busulphan (300 mg/m^2 for 1 day), Cyclophosfamide (1500 mg/m^2 per day for 4 days) and Etoposide (250 mg/m^2 per day for 3 days); Fludarabine (30 mg/m^2 per day for 6 days), Methotrexate (10 mg/m^2 per day for 3 days); induction with 3 cycles of VAD (Vincristine 0.4 mg; Doxorubicine 9 mg/m^2, Dexamethasone 40 mg) followed by high-dose Melphalan (100 mg/m^2 per day for 2 days).

3.2. *Cognitive functions over time*

Table 2 shows the mean standardised neuropsychological test scores for all time points. At baseline, between-group differences in mean scores and the measure of overall cognitive functioning were not observed. At follow-up, however, mean scores in the HSCT group were significantly lower for several measures of attention and executive function, and psychomotor function compared to the REF group.

Four RRM models were generated to evaluate changes in cognitive functions over time. Composite scores of the cognitive domains were entered as dependent variables. Time trend was entered as linear and quadratic time (time^2) terms. Error variance was declared unstructured and age, gender and education were entered as covariables. Interaction terms (time × group, time × gender, time × age, time × dropouts, time^2 × dropouts, group × dropouts) were considered as random, and only maintained when the models significantly improved. Based on fit statistics, the model that included all covariables and interaction terms was selected for interpretation.

For all cognitive domains, linear and quadratic time terms were not significant, suggesting no change in functioning over time for the entire sample. Interactions between time and group showed significant negative slopes for attention and executive function ($P = 0.01$) and for psychomotor function ($P = 0.03$), indicating a mild time-dependent decline in functioning over time for the HSCT group compared to the REF group (Table 3). Covariate adjustment showed interaction effects of age, female gender (negative), and education (positive) for several cognitive domains, and primarily demonstrated poorer performance over time in attention and executive function for older patients ($P = 0.01$). Further statistical analyses revealed that TBI for conditioning contributed to poorer psychomotor function at follow-up ($P = 0.02$). In addition, there was a trend for patients who received TBI to have lower scores on the measure of overall cognitive functioning ($P = 0.07$).

Details of HRQOL data are listed in Table 4. HSCT patients had lower scores on several functioning scales (physical, role and social functioning and global health and quality of life) and more symptoms compared to REF patients. In the HSCT

Table 2 – Standardised neuropsychological test scores across time; mean (SD) and percentages of impaired scores

Measures	HSCT group			REF group		
	Baseline, $n = 101$ (%)	8 months, $n = 64$ (%)	20 months, $n = 55$ (%)	Baseline, $n = 82$ (%)	8 months, $n = 70$ (%)	20 months, $n = 59$ (%)
Verbal memory						
CVLTT	0.12 (1.0), 5	−0.00 (0.0), 5	0.45 (1.0), 4	−0.06 (1.0), 6	0.04 (1.0), 3	0.42 (0.9), 2
CVLTSD	0.04 (1.2), 5	−0.06 (1.0), 6	0.19 (1.0), 0	−0.14 (1.1), 5	0.10 (1.0), 3	−0.14 (1.2), 5
CVLTLD	−0.12 (1.0), 4	0.02 (0.9), 0	0.04 (1.0), 0	−0.19 (0.9), 7	0.16 (1.0), 3	−0.19 (0.9), 7
CVLTC	0.01 (1.1), 4	−0.15 (1.1), 3	0.18 (1.0), 4	−0.11 (1.1), 6	−0.10 (1.0), 3	0.12 (1.1), 5
CVLTR	−0.02 (1.0), 6	**0.50 (0.9)*0**	0.15 (0.8), 2	0.12 (0.8), 2	**0.13 (0.9)*** 0	−0.04 (1.0), 9
Visual memory						
RCFTSD	0.00 (1.3), 10	0.84 (1.2), 2	0.86 (1.2), 4	0.09 (1.2), 6	0.57 (1.4), 4	1.03 (1.3), 3
RCFTLD	−0.03 (1.3), 15	0.72 (1.2), 3	0.82 (1.2), 4	0.09 (1.2), 6	0.49 (1.5), 6	0.95 (1.3), 3
RCFTR	−0.35 (1.1), 10	−0.09 (1.2), 6	0.10 (1.3), 6	−0.19 (1.1), 10	0.15 (1.0), 3	0.36 (1.0), 5
BVRTC	−0.06 (0.7), 2	0.00 (0.7), 0	0.00 (0.8), 4	0.01 (0.7), 1	0.02 (0.7), 3	0.12 (0.6), 0
BVRTE	0.00 (1.0), 8	0.03 (0.8), 2	0.02 (1.0), 10	0.10 (0.8), 2	0.05 (0.9), 6	0.20 (0.8), 2
Attention/executive functions						
CF	0.61 (0.8), 0	0.70 (0.8), 0	0.78 (0.8), 0	0.65 (0.7), 0	0.76 (0.8), 0	0.68 (0.7), 0
WD	0.74 (1.0), 1	0.75 (1.0), 1	0.91 (1.1), 0	0.75 (0.9), 1	0.83 (1.0), 1	0.96 (1.1), 0
TMTA	0.47 (1.3), 4	**0.48 (0.9)**, 0**	**0.87 (1.4)*2**	0.81 (1.4), 2	**1.07 (1.3)**1**	**1.51 (1.3)*, 0**
TMTB	0.64 (1.2), 1	**0.64 (1.3)*3**	**0.57 (1.5)**6**	0.84 (1.3), 2	**1.13 (1.3)*1**	**1.35 (1.4)**, 2**
SCWT3	0.14 (1.1), 0	**0.10 (1.2)*3**	0.51 (1.6), 9	−0.01 (1.0), 1	**0.59 (1.5)*4**	0.82 (1.2), 0
D2GZ	0.35 (1.0), 0	**0.48 (1.0)*0**	0.71 (1.1), 2	0.56 (1.0), 2	**0.91 (1.1)*0**	1.05 (1.2), 0
D2F	1.12 (1.4), 0	1.12 (1.3), 0	1.33 (1.4), 2	0.91 (1.3), 0	1.13 (1.6), 6	1.56 (1.3), 0
D2KL	0.42 (1.7), 10	0.79 (1.6), 5	1.21 (1.6), 4	0.60 (1.8), 10	1.23 (1.7), 4	1.47 (1.8), 5
Visuospatial functions						
RCFTC	0.56 (2.0), 9	0.45 (1.7), 5	0.10 (1.6), 7	0.83 (1.8), 4	0.36 (1.9), 9	0.04 (1.5), 7
WBD	1.20 (1.0), 0	1.55 (1.0), 0	1.54 (1.0), 0	1.20 (0.8), 0	1.49 (0.9), 0	1.62 (0.9), 0
Psychomotor functions						
WDS	1.02 (0.9), 0	**1.04 (1.0)*0**	0.91 (1.1), 0	1.10 (0.8), 0	**1.37 (0.8)*0**	1.43 (0.9), 0
FTD	−0.22 (1.3), 9	−0.47 (1.3), 14	−0.56 (1.4), 13	−0.14 (1.2), 6	−0.31 (1.2), 9	−0.22 (1.2), 7
FTND	−0.47 (1.4), 15	−0.83 (1.4), 21	−1.06 (1.4)*18	−0.45 (1.3), 13	−0.56 (1.2), 17	−0.47 (1.2)* 7
RTTSDT	−0.17 (0.9), 3	−0.37 (0.9), 10	−0.84 (2.4), 17	−0.24 (1.0), 5	−0.34 (1.0), 7	−0.56 (1.1), 10
RTTSMT	−0.39 (1.3), 11	−0.39 (1.4), 7	−0.70 (3.8), 11	−0.31 (1.1), 7	−0.23 (1.0), 6	−0.13 (1.0), 3
RTTCDT	−0.36 (1.3), 10	−0.60 (1.3), 8	−0.64 (1.3), 19	−0.38 (1.5), 12	−0.44 (1.1), 10	−0.53 (1.3), 14
RTTCMT	−0.64 (1.5), 13	−0.67 (1.5), 14	−0.70 (2.2), 15	−0.41 (1.1), 7	−0.38 (1.0), 6	−0.29 (1.0), 7
RTTE	−0.31 (2.0), 11	−0.00 (1.2), 6	−0.29 (1.2)**, 11	−0.03 (1.3), 7	0.14 (1.0), 4	0.22 (0.8)**, 2

Values in bold indicate significant results of $^{*}P < 0.05$ or $^{**}P < 0.01$.

HSCT, bone marrow or haematopoietic stem-cell transplantation; REF, reference. CVLTT = California verbal learning test-total score; CVLTSD = California verbal learning test-short delay recall; CVLTLD = California verbal learning test-long delay recall; CVLTC = California verbal learning test-consolidation; CVLTR = California verbal learning test-recognition; RCFTSD = Rey complex figure test and recognition trial-short delay recall; RCFTLD = Rey complex figure test and recognition trial-long delay recall; RCFTR = Rey complex figure test and recognition trial-recognition; BVRTC = Benton visual retention test-correct score; BVRTE = Benton visual retention test-error score; CF = Category fluency; WD = WAIS digits; TMTA = Trailmaking A; TMTB = Trailmaking B; SCWT3 = Stroop colour word test – colour-word card; D2GZ = D2 test-GZ score; D2F= D2 test-error score; D2KL = D2 test-concentration score; RCFTC = Rey complex figure test and recognition trial-copy; WBD = WAIS block design; WDS = WAIS digit symbol; FTD = Fingertapping-dominant; FTND = Fingertapping-nondominant; RTTSDT = Reaction time test-single decision time; RTTSMT = Reaction time test-single motor time; RTTCDT = Reaction time test-complex decision time; RTTCMT = Reaction time test-complex motor time ; RTTE = Reaction time test-error score.

Table 3 – Estimated intercepts and slopes of time-group effects of the cognitive domains

Cognitive domain	Intercept		Slope		*P*-value
	Estimate	SE	Estimate	SE	
Verbal memory	49.03	4.35	−0.57	0.60	0.35
Visual memory	59.32	4.00	0.09	0.56	0.87
Attention/executive function	54.03	3.42	−0.98	0.37	0.01
Visuospatial function	62.03	4.78	−0.41	0.61	0.50
Psychomotor function	56.58	3.15	−1.31	0.58	0.03

SE, standard error.

Intercepts represent cognitive functions at baseline (estimate in *T*-scores with a mean of 50 and standard deviation of 10) and slopes characterise change in cognitive functions over time.

Table 4 – Health-related quality of life questionnaires; transformed scores, mean (SD)

Measures	HSCT group			REF group		
	Baseline, $n = 101$	8 months, $n = 64$	20 months, $n = 55$	Baseline, $n = 82$	8 months, $n = 70$	20 months, $n = 59$
QLQ-C30						
Physical functioning	74.3 (23.2)	**72.5 (23.8)***	**76.3 (25.2)****	77.1 (19.7)	**82.6 (21.0)***	**87.2 (17.8)****
Role functioning	62.4 (31.1)	**60.7 (27.2)****	**64.5 (29.9)****	69.5 (26.2)	**76.0 (23.0)****	**80.2 (22.4)****
Cognitive functioning	76.5 (10.0)	82.6 (20.5)	82.1 (19.1)	83.5 (17.6)	79.8 (23.7)	82.5 (20.8)
Emotional functioning	**70.2 (28.3)***	82.8 (19.9)	77.7 (22.0)	**79.4 (18.8)***	78.3 (23.4)	82.3 (19.9)
Social functioning	69.2 (29.8)	**70.3 (26.1)***	**75.3 (29.8)***	76.8 (23.4)	**81.4 (25.1)***	**87.4 (18.3)***
Global health	66.7 (23.0)	66.4 (17.7)	**66.4 (22.3)****	66.5 (18.8)	70.5 (18.4)	**79.0 (15.8)****
Global quality of life	71.0 (21.5)	71.9 (22.0)	**70.4 (22.1)***	72.4 (23.4)	74.8 (18.8)	**79.0 (16.7)***
Fatigue	31.9 (25.5)	34.2 (24.3)	**38.1 (26.6)****	38.3 (25.4)	29.5 (20.3)	**25.7 (21.5)****
Nausea/vomiting	5.1 (13.1)	**7.6 (15.1)***	7.1 (14.3)	7.3 (16.2)	**3.1 (7.1)***	2.9 (8.9)
Pain	16.8 (25.2)	15.1 (19.9)	14.4 (23.6)	13.8 (20.3)	16.0 (23.8)	10.9 (21.5)
Dyspnoea	15.3 (20.8)	18.2 (22.9)	22.2 (27.5)	21.9 (25.8)	16.2 (23.2)	16.1 (22.7)
Sleep disturbance	20.7 (28.3)	21.4 (26.8)	**22.8 (28.0)***	19.9 (28.1)	20.5 (24.9)	**11.5 (19.3)***
Appetite loss	7.0 (17.3)	**18.7 (29.6)*****	**16.7 (25.7)****	9.3 (19.1)	**3.3 (10.0)*****	**3.4 (12.0)****
Constipation	4.7 (14.3)	2.6 (9.0)	3.7 (10.6)	3.3 (10.0)	1.9 (7.8)	2.3 (10.6)
Diarrhoea	10.4 (18.8)	6.2 (15.6)	**8.0 (19.4)***	5.7 (15.5)	4.3 (11.2)	**1.1 (6.1)***
Financial impact	14.5 (25.7)	19.3 (26.4)	19.1 (29.4)	9.8 (20.6)	12.9 (24.3)	10.9 (20.1)
QLQ-LEU						
Chills	17.5 (24.0)	**12.0 (21.7)***	12.3 (21.7)	9.9 (17.0)	**5.2 (14.6)***	6.3 (15.9)
Itchy skin	22.3 (30.7)	17.1 (23.0)	17.9 (26.5)	20.6 (30.7)	17.1 (23.9)	11.5 (21.2)
Dry skin	29.7 (28.4)	31.2 (30.8)	**38.9 (31.6)*****	28.4 (25.9)	22.9 (28.1)	**17.8 (22.7)*****
Stiff joints	24.9 (27.0)	34.4 (30.3)	27.8 (28.0)	20.2 (24.0)	25.7 (31.2)	22.4 (28.2)
Feeling cold	24.0 (26.8)	**33.3 (32.0)****	**29.6 (32.8)***	21.4 (28.5)	**19.0 (23.1)****	**16.7 (23.6)***
Flushes	10.4 (20.0)	6.8 (15.9)	5.6 (14.1)	10.7 (21.6)	7.6 (17.2)	8.0 (19.1)
Headache	12.8 (19.5)	12.0 (19.1)	16.0 (23.1)	13.2 (19.5)	15.7 (22.5)	14.4 (21.7)
Hearing loss	6.1 (18.7)	9.9 (21.1)	4.9 (15.1)	3.3 (10.0)	6.7 (16.6)	8.6 (19.3)
Pain during sex	7.1 (17.4)	**14.6 (23.7)***	8.0 (22.4)	6.2 (16.8)	**6.2 (18.2)***	6.9 (17.4)
Fever	**15.2 (25.8)****	6.8 (17.0)	**11.1 (23.3)***	**4.9 (13.0)****	2.4 (8.7)	**3.4 (10.2)***
Infection	15.5 (24.9)	**15.6 (23.7)***	**20.4 (27.0)****	9.5 (18.4)	**7.6 (17.2)***	**6.3 (13.2)****
Weight loss	10.4 (19.4)	**11.5 (17.0)*****	**11.1 (21.5)***	6.6 (17.0)	**2.9 (9.4)*****	**3.4 (12.0)***
Abdominal pain	11.5 (21.9)	8.9 (14.8)	**14.2 (22.0)***	12.8 (20.1)	6.2 (16.3)	**6.3 (13.2)***
Mouth sores	**11.8 (23.5)****	6.2 (13.1)	10.5 (20.3)	**3.3 (12.5)****	5.7 (13.9)	7.5 (15.3)
Pain during urination	1.0 (5.7)	2.6 (9.0)	**3.1 (11.7)***	2.1 (8.1)	.5 (4.0)	**0.0 (0.0)***
Blood in urine	1.3 (8.1)	0.0 (0.0)	0.0 (0.0)	.4 (3.7)	.5 (4.0)	0.0 (0.0)
Sensory loss	18.0 (22.5)	**12.8 (18.7)*****	**9.9 (19.0)***	13.2 (19.7)	**2.4 (6.5)*****	**3.7 (10.4)***
Functional status	**4.4 (12.0)****	2.3 (9.8)	2.2 (9.7)	**.6 (3.2)****	2.1 (8.0)	.9 (4.9)

Values in bold indicate significant results of *$P < 0.05$, **$P < 0\ .01$ or ***$P < 0\ .001$.
HSCT, bone marrow or haematopoietic stem-cell transplantation. REF, reference.
QLQ-C30, EORTC QOL questionnaire; scores range from 0 to 100; higher scores on the functioning scales represent a higher level of functioning; higher scores on the symptom scales and/or items represent more perceived symptoms.
QLQ-LEU, MRC/EORTC QOL leukaemia-BMT module; scores range from 0 to 100; higher scores represent more perceived symptoms.

group, overall cognitive functioning was negatively associated with global health at T3 ($r = -0.41$; $P = 0.002$).

Table 5 shows an overview of subjective cognitive functioning, fatigue and general and cancer-related distress. No significant differences in subjective cognitive functioning were observed between groups at any time point. Physical fatigue levels were higher in HSCT patients at follow-up ($P < 0.05$). More frequent feelings of avoidance of disease were reported in the HSCT group at baseline ($P < 0.05$). No significant differences between groups were found in mean levels of anxiety and depression at any time point, though the number of anxiety cases was higher in the HSCT group at T1 (14% versus 4%; $P < 0.05$). At follow-up, overall cognitive functioning in HSCT patients was weakly associated with anxiety (T3 $r = 0.32$; $P = 0.02$), depression (T3 $r = 0.28$; $P = 0.04$) and feelings of intrusion (T2 $r = 0.30$, $P = 0.02$; T3 $r = 0.31$, $P = 0.01$).

Lastly, work attendance was significantly lower in HSCT patients at follow-up (14% versus 50% at T2, $P < 0.001$; 40% versus 66% at T3, $P = 0.008$).

4. Discussion

The present study in HSCT survivors is the first to compare cognitive functions over time to a disease-specific reference group. Cognitive functions remained stable and are in general identical to those of haematological cancer patients not treated with HSCT. The observed differences in performance are subtle and domain-specific as they are limited to attention to executive function, and psychomotor function. Poorer functioning in psychomotor function at follow-up was related to TBI. The current findings are in accordance with other re-

Table 5 – Overview of subjective cognitive functioning, fatigue and general and cancer-related distress

Measures	HSCT group			REF group		
	Baseline, $n = 101$	8 months, $n = 64$	20 months, $n = 55$	Baseline, $n = 82$	8 months, $n = 70$	20 months, $n = 59$
CFQ total score, mean (SD)	26.2 (12.9)	27.4 (14.3)	28.4 (15.3)	28.0 (14.1)	30.5 (16.6)	30.2 (16.4)
MFI General fatigue, mean (SD)	11.0 (4.7)	12.3 (4.8)	12.0 (4.7)	12.1 (4.4)	11.0 (4.5)	10.5 (4.9)
MFI Physical fatigue, mean (SD)	11.2 (5.0)	**12.4 (4.7)***	**11.3 (4.8)***	12.2 (5.1)	**10.5 (4.6)***	**9.2 (4.5)***
MFI Reduced activity, mean (SD)	10.5 (5.0)	9.7 (4.3)	9.5 (4.0)	11.1 (5.0)	9.2 (4.5)	8.2 (4.6)
MFI Reduced motivation, mean (SD)	8.0 (3.9)	7.3 (3.4)	7.6 (3.9)	8.4 (4.1)	8.2 (4.2)	7.7 (4.0)
MFI Mental fatigue, mean (SD)	9.6 (4.6)	8.9 (4.3)	9.0 (4.6)	9.8 (4.3)	9.4 (4.6)	8.9 (4.7)
IES Intrusion disease, mean (SD)	11.0 (7.5)	9.4 (8.0)	9.1 (8.5)	9.4 (6.7)	8.7 (6.7)	8.6 (6.5)
IES Intrusion treatment, mean (SD)	7.8 (6.9)	8.7 (7.8)	8.4 (8.2)	8.5 (6.7)	6.9 (6.0)	7.2 (6.4)
IES Avoidance disease , mean (SD)	**10.6 (8.9)***	7.8 (8.5)	7.3 (8.7)	**7.4 (7.3)***	7.1 (8.0)	6.1 (5.7)
IES Avoidance treatment, mean (SD)	8.3 (8.4)	7.3 (8.1)	6.7 (8.3)	6.7 (7.3)	6.1 (7.8)	5.5 (5.5)
HADS Anxiety, mean (SD)	5.5 (4.0)	4.3 (3.6)	4.7 (4.0)	4.7 (3.5)	4.6 (3.8)	4.6 (3.4)
HADS Depression, mean (SD)	3.7 (3.4)	3.4 (3.1)	4.2 (3.5)	3.7 (3.5)	4.0 (3.9)	3.3 (3.2)
HADS Anxiety >10, *n* (%)	**14 (14%)***	4 (6%)	5 (9%)	**3 (4%)***	7 (10%)	4 (7%)
HADS Depression >10, *n* (%)	5 (5%)	3 (5%)	4 (7%)	7 (9%)	7 (10%)	2 (3%)

Values in bold indicate significant results of $P < 0.05$.
HSCT, bone marrow or haematopoietic stem-cell transplantation. REF, reference.
CFQ, Cognitive failure questionnaire; total raw scores range from 0 to 100; higher scores indicate more subjective problems.
MFI, Multi-dimensional fatigue inventory; scores range from 4 to 20; higher scores represent more symptoms.
IES, Impact of event scale; scores for intrusion range from 0 to 35 and scores for avoidance range from 0 to 40; higher scores indicate more complaints.
HADS, Hospital anxiety and depression scale; scores range from 0 to 21; higher scores denote more complaints; a cut-off score of >10 was used as an indication for increased levels of anxiety or depression.[34]

ports and suggest that mild cognitive impairment is apparent prior to transplant and primarily affect the aforementioned cognitive domains.[6,8,9,15,16] However, unlike Syrjala and colleagues we found no evidence for a decline in cognitive functions followed by a recovery to pre-transplant levels, as function over time remained stable at follow-up.[16]

Previous studies on cognitive functions in HSCT patients suggested that HRQOL factors may contribute to deficits or changes in cognitive functions over time.[8,9] Our findings provide evidence conversely that affective status has only a minor impact on cognitive functions before and after HSCT, despite significant between-group differences on several HRQOL functioning scales and symptoms at all time points. This is contrary to the results of our previous retrospective study in 40 long-term HSCT survivors who were assessed between 22 and 82 months after transplant. Global health and fatigue were the main predictors of cognitive impairment in these long-term survivors. This inconsistency could be related to the shorter follow-up period in the present study, and emphasises that further follow-up in the current cohort of patients is necessary.

A few limitations impact the interpretation of the current findings. First, a possible selection bias could have been introduced as 22% of HSCT patients and 14% of REF patients declined to participate. Additionally, the high attrition rate in the HSCT group, caused by (post)transplant complications, may have contributed to this bias. Second, despite the relatively large sample size, there was heterogeneity in the patient groups (e.g. wide variety of diagnosis and treatment). This may have influenced associations between disease- and treatment-related factors and cognitive functions. Last, a true baseline, before the start of any treatment, or even prior to the start of the disease is desirable but of course not feasible.

In conclusion, this first longitudinal study on HSCT with a disease-specific reference group shows the absence of clinically significant treatment-related changes in cognitive functions up to 20 months after treatment. Further long-term follow-up of this cohort is indicated to examine possible future cognitive changes within these particular domains. At this point in time, however, it is legitimate to consider HSCT as a treatment without severe side-effects on cognitive functions compared to the standard non-myeloablative therapies for haematological malignancies.

Conflict of interest statement

The authors declare to have no conflicts of interest.

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