Cognitive Functioning and Quality of Life in Long-Term Adult Survivors of Bone Marrow Transplantation

Helena Harder, M.Sc.[1]
Jan J. Cornelissen, M.D.[2]
Arthur R. Van Gool, M.D.[3]
Hugo J. Duivenvoorden, M.D.[4]
Wil M. H. Eijkenboom, M.D.[5]
Martin J. van den Bent, M.D.[1]

[1] Department of Neuro-Oncology, University Hospital Rotterdam/Daniel den Hoed Cancer Center, Rotterdam, The Netherlands.

[2] Department of Hematology, University Hospital Rotterdam/Daniel den Hoed Cancer Center, Rotterdam, The Netherlands.

[3] Department of Psychosocial Oncology, University Hospital Rotterdam/Daniel den Hoed Cancer Center, Rotterdam, The Netherlands.

[4] Department of Medical Psychology and Psychotherapy, Erasmus University Rotterdam, Rotterdam, The Netherlands.

[5] Department of Radiotherapy, University Hospital Rotterdam/Daniel den Hoed Cancer Center, Rotterdam, The Netherlands.

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Address for reprints: Helena Harder, M.Sc., Department of Neuro-Oncology, University Hospital Rotterdam/Daniel den Hoed Cancer Center, P.O. Box 5201, 3008AE Rotterdam, The Netherlands; Fax: 011-44-31-10-4391031; E-mail: harder@hemh.azr.nl

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BACKGROUND. The late neurotoxic effects of bone marrow transplantation (BMT) on cognitive functioning and quality of life (QOL) were investigated in a consecutively treated cohort of long-term adult survivors.

METHODS. Progression-free patients treated with BMT or peripheral stem cell grafts for a hematologic malignancy at least 2 years before study participation were examined with a comprehensive battery of neuropsychological tests and questionnaires for QOL and mood states. The results of the neuropsychological tests were compared with healthy population norms.

RESULTS. Forty patients were included, 87.5% of whom had undergone an allogeneic transplantation. All received total body irradiation up to 12 Gy (in two fractions). Assessment took place 22–82 months after BMT. Mild to moderate cognitive impairment was found in 24 patients (60%). Compared with healthy population norms, selective attention and executive function, information processing speed, verbal learning, and verbal and visual memory were most likely to be affected. The mean score for the total patient group revealed that these patients scored significantly lower on the information processing speed task compared with expected scores obtained from the normal population. The main predictors for poor neuropsychological performance were fatigue, global health, and educational level. Other correlations with moderate to severe cognitive impairment were subjective cognitive complaints, physical functioning, social functioning, overall mood states, and employment status.

CONCLUSIONS. These data indicate that BMT may lead to cognitive complaints and late cognitive deficits in long-term adult survivors. Cognitive functioning should therefore be used as an outcome parameter in BMT studies. ***Cancer* 2002;95: 183–92.** © *2002 American Cancer Society.*

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Autologous or allogeneic bone marrow (BMT) or stem cell transplantation has become standard treatment for a variety of hematologic malignancies. Because this treatment is curative for an increasing number of patients, attention has turned to the long-term effects of BMT. Unfortunately, the BMT procedure still carries considerable morbidity as a consequence of acute and delayed disease and treatment-related complications. These patients are at risk of developing neurologic complications and delayed encephalopathies, which are associated with the BMT conditioning regimen.[1–7] The BMT conditioning regimen involves high-dose chemotherapy, often combined with total body irradiation (TBI). Both high-dose chemotherapy and radiation therapy to the brain are known causes for delayed central nervous system (CNS) toxicity.[8–11] Other potential severe

treatment-related complications are opportunistic infections related to immunosuppression, extensive acute or chronic graft versus host disease (GVHD), side effects of immunosuppressive therapy (cyclosporine [CyA], methotrexate, or corticosteroids), or major organ failure. These may give rise to a variety of severe neurologic complications, in particular (drug-induced) encephalopathies and opportunistic CNS infections.[6] Intrathecal chemotherapy or whole brain irradiation before or after BMT as treatment or prophylaxis for CNS disease may also induce delayed leukoencephalopathy.[12,13] The presence of this combination of potential risk factors for late neurologic sequelae makes the BMT procedure unique compared with other potentially neurotoxic forms of cancer treatment. The impact, however, of the mentioned risk factors on cognitive functioning in long-term survivors is not well documented. Neuropsychological studies in cancer patients treated with only one of the treatment forms used in the BMT conditioning regimen showed evidence of cognitive impairment.[14–18] The few previous reports on the specific neurocognitive side effects of BMT suggest that these patients are at risk to develop cognitive deficits.[5,19–26] Only five studies focused on the late side effects but methodologic shortcomings, such as lack of neuropsychological testing, small sample size, or selection of patients, preclude reliable conclusions.[5,19,20,25,26] We have, therefore, assessed cognitive functioning and quality of life (QOL) in a consecutively treated cohort of long-term adult survivors of BMT. A minimum time interval of 2 years posttreatment was used to elude the influence of acute side effects of BMT.

MATERIALS AND METHODS

Patient Selection

Patients treated with BMT for hematologic malignancies 2–7 years before the time of this study were selected from the BMT database of the Department of Hematology. In this 5-year period, 141 patients were treated with a BMT conditioning regimen involving both high-dose chemotherapy and TBI. Of these, a cohort of 61 consecutive long-term survivors was identified.

Patients eligible for our study had to meet the following inclusion criteria: 1) no evidence of recurrent disease, 2) no previous neurologic or psychiatric disorders, 3) no use of psychoactive drugs or medication known to affect cognitive functioning, 4) no history of or current substance abuse, 5) basic proficiency of the Dutch language, 6) between 18 and 65 years of age.

Measures

Cognitive performance was assessed by a comprehensive battery of standardized neuropsychological tests. Before testing, the patients were interviewed with regard to cognitive problems experienced in their daily routine. The extent of the problems was rated by the neuropsychologist on a 4-point Likert-type scale (0 = no problems, 1 = mild problems, 2 = moderate problems, 3 = severe problems).[27] In addition, a set of self-administered questionnaires was applied to collect data on QOL and mood states. Ratings of a widely used mental status screening test, the Mini Mental State Examination (MMSE), and the Karnofsky performance status (KPS) scale were obtained before the assessment.[28,29]

The neuropsychological evaluation consisted of 11 internationally used psychometric tests selected for validity and availability of normative data. The battery was designed to assess several cognitive functions: general intelligence and conceptual reasoning, verbal function, memory, attention functions and concentration, executive functions, visuospatial and visuoconstructive ability, psychomotor function, and speed of information processing.

The Groninger Intelligence Test, short form (GIT-V)

The GIT-V[30] measures actual general intelligence level. The test consists of three subtests for, respectively, spatial ability, abstract reasoning, and arithmetic. The scores of the three subtests are transformed into an intelligence quotient (IQ) based on age and gender.

The National Adult Reading Test (NART)

The NART[31] estimates premorbid intelligence based on verbal ability. This is measured by the ability to read aloud correctly a list of phonetically irregular words and the accuracy of oral pronunciation is scored. Premorbid intelligence can be estimated by the NART as vocabulary level and related verbal skills correlate with overall ability level.[32]

Wordfluency test

The Wordfluency test[30] evaluates language processing by naming as many words as possible belonging to two word categories. The score is the sum of words produced in each trial.

California Verbal Learning Test (CVLT)

The CVLT[33] assesses verbal memory capacities. The test consists of five presentations with recall of a 16-word list, one presentation of a second 16-word list and recall, followed by a short-term free recall and

cued recall of the first list. Retention is tested 20 minutes after learning by delayed free recall, delayed cued recall, and recognition. The CVLT also provides information on learning strategies and retroactive and proactive interference tendencies.

Rey Complex Figure Test (CFT)

The CFT[34] measures both visuospatial organization and visual memory. The patient is asked to copy a complex figure. Immediate recall is assessed 3 minutes after copying. Evaluation of the immediate recall is obtained by using scores based on a unit scoring system referring to specific details of the figure.

Digit Span of the Wechsler Adult Intelligence Scale

The Digit Span[35] assesses immediate recall and attention. The patient is asked to repeat successive series of digits in two conditions, forward and backward.

Trailmaking Test (TMT)

The TMT[36] measures psychomotor speed and attention. The test consists of small randomly printed consecutively numbered circles (Part A) and consecutively numbered and lettered circles (Part B). The patient has to draw lines to connect the circles, and in Part B alternating between the two sequences is required. Slow performance on one or both parts of the test indicates cognitive deterioration.

Stroop Color Word Test (SCWT)

The SCWT[37] determines selective attention and executive functions. In Parts A and B, the time needed to complete reading 100 color names and naming 100 colored rectangles is recorded. Part C involves 100 color names in different printing ink than the color name; the speed at which the color of the printing ink is named is taken as the test variable and is recorded. The time taken to complete each part and the total number of failures are registered.

Fingertapping task

The Fingertaping task[32] measures psychomotor speed. The patient is asked to press a marked button with the index finger of each hand separately as fast as possible for 1 minute. The number of hits in the first and second half (30 seconds) of the test and the number of total hits is recorded.

Reaction time task

The reaction time task[38] measures the speed of information processing in two single stimuli tasks (visual and acoustic) and two complex binary choice tasks. The use of a rest button and a reaction button enables breakdown into decision-making time and motor time. Decision time, motor time, and the number of missing, incorrect, or incomplete responses are scored.

Questionnaires of QOL and Mood States

QOL was measured with the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30.[39] This instrument includes five domains that assess functioning (physical, role, cognitive, emotional, social) by using multiitem scales, two domains that assess global health status and global QOL, and nine multiitem scales or single items that assess symptomatology. In conjunction with the EORTC QLQ-C30, we used the EORTC brain cancer module (BCM 20) to screen for neurologic dysfunction.[40] The BCM 20 contains four multiitem scales (future uncertainty, visual disorder, motor dysfunction, and communication deficit) and seven single items.

A questionnaire of mood states was administered to distinguish between cognitive deficits related to BMT treatment or to additional psychological distress. The brief version of the Profile of Mood States (POMS) was used as a summary measure.[41,42] The POMS has separate subscales for five dimensions of general psychological distress: depression, tension, anger, fatigue, and vigor. Thirty-two items are scored on a 5-point Likert-type scale format, ranging from 0 to 4.

Procedure

The study was approved by the institutional ethics and scientific committee and written informed consent was obtained from all patients. The medical records of the patients were examined by a physician to record information regarding patients' current medical status (including current medication use) and history of disease and treatment (e.g., cytotoxic treatment and complications of the BMT conditioning regimen). All psychometric tests were administered in the same order for all patients and scored by an experienced neuropsychologist. The assessment took approximately two and one-half hours to complete.

Statistical Methods

The questionnaires were transformed into scores according to standard procedures. Before computing a total score for overall psychological distress, the total POMS score, the scores of the positive psychological distress subscale Vigor were transformed so they were in line with the scores of the negative psychological distress subscales. The total POMS score was computed by summing the standard z-scores for each subscale and then dividing this score by the number of subscales. The total POMS score was considered ab-

errant when the score was 2 standard deviations (SDs; $z \leq -2.0$) below the mean of the healthy population norms.[41] The raw data of each neuropsychological test (or test indices) were converted into standard (z-scores) and percentile scores by using age and gender-corrected healthy population norms. Patients were classified according to the commonly accepted standard criteria of each test (i.e., impaired either when test scores were 2 SDs [$z \leq -2.0$] below the mean of the standard scores [$z = 0$] or below percentile 10). General intelligence was considered to be aberrant if the difference between the estimated premorbid and actual IQ was more than 20 points ($z \leq -2.0$), taking into account that the NART underestimates premorbid intelligence by 15 IQ points.[31,43] A composite score for cognitive impairment was computed for each individual by counting all test indices on which the patient was impaired.

The mean score of each neuropsychological test was computed after transforming all test scores into percentile scores (to ease interpretation). In a normal population, a percentile score of 50 means that the patient has an average test result; the SD is 34. The differences between the distribution of the observed frequencies and the distribution of the expected frequencies were tested with a chi-square test (χ^2 for trend). The distribution of the expected frequencies was calculated using the scores of the normal population as reference group.[30,32–38] The upper and lower cells were collapsed so that the percentage of cells with an expected count less than 5 did not exceed the limit of 20%.

Descriptive statistics were performed for all variables. Differences in individual test scores in various patient groups defined by demographic and disease and treatment-related parameters were analyzed by the Student t test. Relationships among overall cognitive performance, psychosocial functioning, and subjective measures of cognitive complaints were analyzed using Pearson's correlation coefficients.

Multiple linear regression analysis was used to estimate the influence of disease and/or treatment-related variables on cognitive impairment. The set of variables to enter the analysis were selected by the method of multiple regression; the composite score for cognitive impairment was used as the dependent variable. The standardized regression coefficient (β) was used as a measure of relative importance.

Tests were two-sided and a P value of 0.05 or less was considered statistically significant. All data were analyzed using the Statistical Package for Social Sciences (SPSS) Windows 9.0 software.

TABLE 1
Patient Characteristics (n = 40)

	No. of patients	Mean (SD)	Range
Gender			
Male	24		
Female	16		
Age (yrs)		40.8 (10.3)	18–60
Age at BMT (yrs)		37.2 (10.4)	15–55
Time since BMT (mos)		45.1 (17.3)	22–82
Estimated premorbid IQ		105.3 (10.0)	84–126
Educational level			
Less than high school degree	3		
High school degree	14		
Vocational/trade school	10		
College/bachelors degree	7		
Graduate/professional degree	6		
Diagnosis			
Acute lymphocytic leukemia	8		
Acute myelogenous leukemia	10		
Chronic myelogenous leukemia	6		
Non-Hodgkin lymphoma	6		
Myelodysplastic syndrome	4		
Multiple myeloma	4		
Aplastic anemia	2		
Intrathecal treatment			
Yes	11		
No	29		
Type of BMT			
Allogeneic MRD	26		
Allogeneic MUD	9		
Autologous	5		
Conditioning regimen			
CP	12		
Ara-C + CP	19		
VP-16 + CP	9		
TBI dose (Gy)			
10 (two fractions)	13		
12 (two fractions)	25		
8.5 (two fractions)	1		
8 (one fraction)	1		

BMT: bone marrow transplantation; IQ: intelligence quotient; MRD: matched related donor; MUD: matched unrelated donor; CP: cyclophosphamide; Ara-C: cytosine arabinoside; VP-16: etoposide; TBI: total body irradiation.

RESULTS

Demographic and Clinical Patient Characteristics

Forty-two patients were eligible for study, 40 (95%) of whom provided written informed consent (1 patient was living abroad temporarily and 1 patient declined to participate). Ten patients were excluded because of recurrent disease or secondary malignancies as were six more because they lacked a basic proficiency of the Dutch language. Two patients were excluded due to long-term alcohol and/or drug abuse and one because of recurrent depressive episodes and use of psychotropic drugs. Demographic and clinical information is shown in Table 1.

The two patients with aplastic anemia did not receive induction therapy before the BMT procedure. CNS prophylaxis was given to 11 patients before BMT (four to eight injections of intrathecal methotrexate or cytosine arabinoside [ara-C]), which was continued (two to three injections) in five patients after the BMT procedure. One patient received low-dose TBI (24 $\times$ 0.10 Gy) before undergoing the BMT conditioning regimen. Neurologic complications before BMT were found in two patients: one patient had CNS disease and was treated with cranial radiotherapy (16 $\times$ 1.5 Gy), another patient had seizures related to intrathecal treatment.

All patients underwent conditioning with high-dose chemotherapy and TBI. High-dose chemotherapy consisted of cyclophosphamide, either alone (60 mg/kg of body weight per day for 2 days) or in combination with ara-C (1000 mg/m^2 per day for 2 days) or etoposide (350 mg/m^2 per day for 2 days). For the majority of patients, high-dose chemotherapy was followed by 10 or 12 Gy of TBI, administered in two doses of either 5 or 6 Gy in 2 days. After the conditioning regimen, most patients (87.5%) received bone marrow support from a related or unrelated donor.

Various regimens for prophylaxis of GVHD were utilized depending on the protocol and the compatibility of the donor. Thirty-four patients received CyA (mean 166.2 days, SD 116.5, range 42–507) and T-cell depletion of the donor graft was performed in 33 patients. One-half of the patients received corticosteroids as immunosuppressive therapy (mean 139.8 days, SD 170.8, range 3–598). The median time interval between BMT and testing was 43 months.

Medical Status and Treatment-Related Neurologic Complications

After the BMT procedure, complete remission of disease was achieved in 36 patients. Four patients with multiple myeloma had partial remission of disease, three of whom used a maintenance dose of interferon-α. Following BMT, 69% of the allogeneic recipients experienced acute GVHD (Grade I–III) and 29% developed mainly limited chronic GVHD (Table 2). Four patients had received treatment for recurrent disease (e.g., donor buffy coat infusion or chemotherapy) and were again responding. All additional therapy was given at least 1 year before neuropsychological testing.

The severe neurologic complications induced by the BMT conditioning regimen are summarized in Table 2. A history of neurologic complications such as encephalopathy, cerebrovascular events, or cerebral infections was found in almost one fourth of this cohort. Fifteen patients underwent cranial magnetic resonance imaging (MRI) at the time of presence of clinical neurologic signs. Abnormal neuroradiologic findings (e.g., white matter abnormalities or focal lesions) were present in seven patients. No current neuroradiologic information was available at the time of neuropsychological evaluation.

TABLE 2
Treatment-Related Complications: GVHD and Neurologic Disorders

Acute GVHD	No. of patients	Chronic GVHD	No. of patients
Grade I	12	Limited	9
Grade II	6	Extensive	1
Grade III	6		
Grade IV	—		
CyA encephalopathy	3		
Hypertensive encephalopathy	1		
Intracerebral hemorrhage	1		
Viral meningoencephalitis	1		
Cerebral toxoplasmosis	1		
Pneumococcal meningitis and cerebral toxoplasmosis	1		
Unspecified cerebral lesion with seizures	1		

GVHD: graft versus host disease; CyA: cyclosporine.

TABLE 3
Subjective Cognitive Problems in Daily Life Routine[a]

	Memory (%)	Attention (%)
No problems	37.5	50
Mild problems	35	32.5
Moderate problems	25	17.5
Severe problems	2.5	—

[a] Information based on a short pretest interview and rated on a scale by the neuropsychologist.

Clinical Performance and Cognitive Screening

Mean performance status (KPS) was 89.8 (SD 10.0, range 70–100); 12 patients had a clinical performance below 90. The screening test of mental status revealed no abnormalities as all patients scored above the MMSE cutoff score of 23 points (mean 28.3, SD 1.1, range 26–30).

Subjective Cognitive Problems in Daily Life Routine

The incidence of reported subjective cognitive problems interfering with daily life routine rated by the neuropsychologist is shown in Table 3. Most patients reported no problems or only very mild problems. However, almost 28% experienced moderate to severe memory problems and 17.5% showed moderate problems in attentional functions. The experienced cognitive problems included difficulties in concentrating

TABLE 4
Neuropsychological Tests: Percentage of Impaired Patients and Mean Test Score

	Impaired patients (%)	Mean test score (SD)[a]	*P* value[b]
Cognitive domain			
Neuropsychological test			
Intelligence			
Groninger Intelligence Test	5	71.43 (28.22)	0.002
Language			
Wordfluency test	0	74.95 (20.24)	0.001
Memory			
California Verbal Learning Test	15		
Total words		43.49 (30.97)	0.48
Learning speed		41.81 (31.06)	0.43
Consolidation		46.59 (29.13)	1.0
Rey Complex Figure Test-recall	20.5	50.26 (31.85)	0.10
Attention and executive function			
Stroop ColorWord Test	23.1		
Word card		46.54 (30.89)	0.97
Color card		46.41 (29.33)	0.88
Color-word card		40.90 (27.86)	0.30
Digit Span	0	61.45 (23.38)	0.01
Trailmaking Test A	0	63.91 (23.01)	0.01
Trailmaking Test B	0	60.00 (24.19)	0.10
Visuospatial organization			
Rey Complex Figure Test-copy	2.6	91.15 (20.50)	0.001
Psychomotor speed			
Fingertapping task	2.5		
Dominant hand		50.40 (29.51)	0.48
Non-dominant hand		49.40 (29.83)	0.08
Speed of information processing			
Reaction time task	32.5		
Single choice task		11.20 (15.56)	0.001
Complex choice task		11.29 (20.65)	0.001

[a] In percentiles (mean = 50, SD = 34).
[b] Compared with expected scores obtained from the reference group.

during conversations or during (paper) work or difficulties in remembering information or appointments. In most cases, the patients experienced a decline in comparison to their level of cognitive functioning before BMT treatment.

Neuropsychological Assessment

Only one patient could not perform all neuropsychological tests due to severe cataract. All other patients completed the battery of neuropsychological tests including the questionnaires. Table 4 presents the percentage of patients who performed in the impaired range on the 11 neuropsychological tests and the mean test score for the total patient group. The distribution of the composite score for cognitive impairment is summarized in Table 5. Sixty percent scored in the impaired range on at least one neuropsychological test. Five patients (12.5%) scored in the impaired range on 3 or more of the 11 tests they completed.

TABLE 5
Overall Cognitive Status: Composite Status: Composite Score for Cognitive Impairment

	No. of patients (%)
No test in impaired range	16 (40)
One test in impaired range	14 (35)
Two tests in impaired range[a]	5 (12.5)
Three tests in impaired range	3 (7.5)
Four tests in impaired range	2 (5)

[a] Including the patient who completed only six neuropsychological tests.

Compared with the normative data of each neuropsychological test, the following domains of cognitive functioning were impaired most frequently: selective attention and executive function (SCWT: $\chi^2 = 6.94$, $df = 1$, $P = 0.008$), information processing speed (reaction time task: $\chi^2 = 162.35$, $df = 1$, $P < 0.001$), visual memory (Rey CFT recall: $\chi^2 = 4.44$, $df = 1$, $P = 0.035$), and verbal learning and memory (CVLT: $\chi^2 = 25.64$, $df = 1$, $P < 0.001$). Verbal functions, intellectual functioning, motor speed, immediate verbal memory, and perceptual organization were unaffected. However, when the distribution of the observed test scores was compared with the distribution of the expected test scores, only the scores on the test for information processing speed were far below those obtained from the reference group (Table 4). The test scores on tests for verbal memory (CVLT) and selective attention (SCWT) were slightly lower but not significant. On several neuropsychological tests, the scores were higher than the expected scores, namely, on the GIT-V, the Wordfluency Test, Digit Span, the Trailmaking A, and the copy of the Rey CFT.

Attendance at work or at school (full-time or part-time) was established in 47% of the patients. Forty percent of the patients were still on disability or sickness benefit although this is influenced by premorbid employment history and complementary disability or unemployment insurance. There was a relation between current employment status and the composite score for cognitive impairment ($r = 0.42$; $P = 0.02$), as well as the incidence of subjective cognitive complaints measured by the EORTC QLQ-C30 ($r = -0.57$; $P = 0.001$), and self-reported memory problems rated by the neuropsychologist ($r = 0.53$; $P = 0.002$).

A multiple linear regression analysis (adjusted for age and gender) was carried out using a selected set of variables as covariates and the composite score for cognitive impairment as the dependent variable. Examination of the standardized regression coefficients

(β) for the individual variables indicated that the strongest predictors of the proportion of impaired tests were fatigue rated with the EORTC QLQ-C30 (β = 0.43; P = 0.03), global health of the EORTC QLQ-C30 (β = 0.55; P = 0.004), and higher educational level (β = 0.29; P = 0.04). Other potential predictor variables like age, global QOL, the total POMS score, type of BMT, dose of TBI, use of CyA, use of T-cell depletion, use of corticosteroids, use of interferon-α, time since treatment, exposure to intrathecal treatment or treatment for recurrent disease, presence of acute or chronic GVHD, presence of pretreatment or posttreatment CNS complications, and the presence of MRI-confirmed abnormal neuroradiologic findings did not account for the variance in the proportion of impaired tests.

QOL and Mood States

The results of the questionnaires for QOL and psychological distress measured by the EORTC QLQ-C30 and the brief POMS are listed in Table 6. Global QOL in this cohort of patients seems satisfactory (mean 82.5, SD 18.1). The cognitive function scale of the EORTC QLQ-C30 (Q20 and Q25) is of special interest in this study. The cognitive function scale was strongly correlated with the symptom fatigue (r = −0.55; $P < 0.001$). The composite score for cognitive impairment was associated with several functional scales or items of the EORTC QLQ-C30: the physical function scale (r = −0.44; P = 0.005), the cognitive function scale (r = −0.58; $P < 0.001$), the social function scale (r = −0.38; P = 0.016), and the symptom fatigue (r = 0.37; P = 0.02).

High levels of current distress ($z \leq -2.0$ in comparison to healthy population norms) in one or more subscales of the brief POMS were found in 15patients. Most of these patients (60%) had a high score on only one of the fivesubscales of the brief POMS, especially on the subscale anger. The total POMS score was aberrant in only three patients and was associated with the composite score for cognitive impairment (r = 0.39; P = 0.02). Further analysis showed a substantial correlation between the composite score of cognitive impairment and the subscale fatigue (r = 0.51; $P <$ 0.001) and a weak correlation with the subscale tension (r = 0.34; P = 0.03).

Absence from work or school was associated with the following factors: fatigue measured by the brief POMS (r = 0.62; $P < 0.001$) and the EORTC QLQ-C30 (r = 0.46; P = 0.01) and physical functioning (r = −0.41; P = 0.021).

TABLE 6
Scores of the Questionnaires of Quality of Life and Mood States

	Mean (SD)
EORTC QLQ-C30[a]	
Functional scales	
Physical function	80.6 (18.4)
Role function	83.8 (22.2)
Cognitive function	74.2 (22.3)
Emotional function	79.2 (24.5)
Social function	72.9 (31.3)
Global health	80.0 (17.4)
Global quality of life	82.5 (18.1)
Symptom scales and/or items	
Fatigue	27.5 (18.7)
Nausea and vomiting	4.2 (11.2)
Pain	12.9 (18.3)
Dyspnea	14.2 (21.2)
Sleep disturbances	18.3 (22.6)
Appetite loss	5.8 (18.3)
Constipation	4.2 (17.2)
Diarrhea	4.2 (13.5)
Financial impact	15.0 (28.2)
EORTC BCM 20[a]	
Multiitem scales	
Future uncertainty	17.8 (19.2)
Visual disorder	11.9 (16.8)
Motor dysfunction	7.2 (10.5)
Communication deficit	17.2 (23.6)
Items	
Headaches	19.2 (23.7)
Seizures	0.8 (5.3)
Drowsiness	10.8 (15.8)
Bothered by hair loss	4.2 (11.2)
Bothered by itchy skin	29.2 (32.2)
Weakness of both legs	13.3 (21.2)
Trouble controlling bladder	5.0 (14.2)
POMS[b]	
Depression	4.3 (5.8)
Anger	8.4 (6.6)
Fatigue	6.1 (5.3)
Vigor	12.6 (3.5)
Tension	5.2 (4.9)

[a] European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, EORTC BCM 20: scores range from 1 to 100; higher scores on the function scales represent a higher level of functioning; higher scores on the symptom scales and/or items represent more perceived symptoms.

[b] Profile of Mood States (POMS): scores range from 0 to 32 (depression), 0 to 28 (anger), 0 to 24 (fatigue and tension), and 0 to 20 (vigor); higher scores indicate greater current mood disturbances except for the subscale vigor.

DISCUSSION

Long-term survivors of BMT are at risk for cognitive impairment as a result of exposure to a number of potentially neurotoxic agents, including those used in the conditioning regimen (e.g., high-dose chemotherapy and TBI), as well as those used as prophylaxis or treatment of GVHD or immunosuppression. Likewise, intrathecal chemotherapy and whole brain irradiation,

often used as prophylaxis and treatment for CNS disease involvement before the BMT conditioning regimen, are risk factors for the development of cognitive deficits. In our study, we analyzed cognitive functioning in a consecutively treated sample of long-term adult survivors of mostly allogeneic BMT with a mean time interval between treatment and neuropsychological testing of more than 3 years. To our knowledge, this is the first study to examine long-term survivors of BMT, who attained a survival period of at least 2 years, with both an extensive battery of neuropsychological tests and measures of QOL and mood states. As anticipated, we observed late cognitive sequelae in a significant percentage of patients. Most patients had only mild cognitive impairment, but five patients (12.5%) showed moderate to severe decreased performance on several neuropsychological measures compared with the normative data. Cognitive dysfunction in these patients was most profound in visual memory, verbal learning and verbal short-term and long-term memory, attention or executive functions, and speed of information processing. When comparing the distribution of observed and expected test scores, a few tests had a lower mean score than expected, but this was only significant for the speed of information processing task. Several neuropsychological tests showed a higher mean score compared with the reference group which is probably related to a higher level of premorbid intelligence (estimated by the NART) in this patient group. Measures of QOL and mood states revealed that the majority of patients reported satisfactory global QOL (median 83.3) and showed no signs of severe mood disturbances.

Only nine studies have been published regarding cognitive functioning in adult BMT patients, five of which explored the neurocognitive status in long-term survivors a year or more after their treatment.[5,19–26] The first study in adult long-term survivors was performed by Parth et al.[19] In a longitudinal design with a follow-up period up to a year posttreatment, the cognitive and motor performance of 44 BMT patients was compared with the cognitive status of their relatives or donors. Cognitive changes in comparison to baseline levels and controls were most profound near the beginning of treatment and involved associative memory, perceptual speed, and logical reasoning. These findings, however, reveal mainly the acute side effects of BMT treatment as the sample size at the last follow-up was reduced to just 11 patients.

Two retrospective studies with an interval between treatment and assessment similar to that of our current study found evidence for cognitive decrement.[5,20] Andrykowski et al.[20] reported slowed cognitive processing, attention problems, and difficulties in reasoning in 30 allogeneic transplant patients and found an association with increased TBI dose. Reduced memory function after allogeneic BMT related to older age, a longer interval post-BMT, chronic GVHD, and long-term CyA use was found by Padovan et al.[5] However, both studies lacked comprehensive neuropsychological testing as only subjective and unreliable measures (self-report questionnaires and a structured interview) were used. Therefore, the extent of cognitive problems may have been misjudged or underestimated.

Two recent studies showed only minor cognitive problems following autologous BMT, which is contradictory to our findings.[25,26] Peper et al.[25] used standardized neuropsychological tests in a small cross-sectional study of 20 survivors of autologous BMT at a mean interval of 32 months after treatment. Only a slight reduction of memory function was found, but these survivors were compared with control patients with renal insufficiencies in whom cognitive dysfunctions are to be expected.[44,45] The same group found normal pretreatment results and improved test performance in a prospective evaluation of 58 autologous BMT patients with a mean follow-up of 27 months.[26] The improvement in cognitive functioning was explained by practice effects of the repeated measurements (before treatment, the first day of TBI, and 6–36 months after TBI/BMT treatment), as well as by an increase of positive mood states. A possible explanation for the inconsistency between these studies and our findings is the difference in the type of BMT. In our study, the majority of patients received allogeneic BMT, 26% of whom had an unrelated donor. The incidence of neurologic complications varies among types of BMT with allogeneic BMT, in particular BMT with unrelated donors, carrying more treatment-related morbidity than autologous BMT.[3–6] In our cohort of patients, the neurotoxity and cognitive dysfunctions will have been more severe because of their exposure to acute and chronic GVHD and complications related to immunosuppression or immunosuppressive therapy. However, we did not find a relationship between the neurologic complications and cognitive impairment. This could be related to the small sample size, as Padovan et al.[5] reported in 66 patients more neurologic and neuropsychological abnormalities after allogeneic BMT compared with autologous BMT. Another explanation for this absence is that some neurologic complications were fully reversible like CyA and other metabolic encephalopathies.

We compared patients' performance on the neuropsychological tests with subjective cognitive problems in their daily life routine. There was a relationship between cognitive impairment and cognitive

problems measured by the EORTC QLQ-C30, but there was no association with the extent of cognitive problems rated by the neuropsychologist before testing. This finding is interesting and suggests that an interview by a clinician without formal neuropsychological testing is an unreliable measure for addressing cognitive functioning in BMT patients.

Our data suggest correspondence between impaired cognitive function and educational level, especially higher educational background. Parameters such as age, gender, and level of education influence cognitive functioning. In particular, education level can affect the level of performance on tasks involving verbal skills, stored information, and other school-related activities.[32] Although the normative data usually have corrections for age and gender, education-specific norms are not available for the majority of neuropsychological tests. Only a longitudinal study in which patients are followed in time and are tested before treatment will overcome this problem.

We also collected information regarding QOL and mood states. An important finding is that fatigue and global health are the main disease and treatment-related predictors for cognitive impairment. Our results on QOL confirm earlier studies among long-term BMT survivors, i.e., up to 10 years following treatment, a considerable percentage of patients still experience a wide range of lingering complaints.[46–48] Physical limitations or functional disability, pain, sexual problems, fatigue, sleep disturbances, and social problems were the most common reported complaints. Our findings show that both global QOL and fatigue were significantly associated with depressed mood measured by the brief POMS. This suggests that these lingering complaints have a great impact on patients' daily life in general. It is still unknown whether the cohesion among fatigue, global health, and cognitive impairment is possibly related to another unspecified factor. It may be worthwhile to investigate whether intervention programs developed specifically to enhance QOL and to reduce fatigue and other late physical effects help patients to reestablish their daily life routine after the BMT treatment.

Our study is the first to evaluate late cognitive side effects using an extensive neuropsychological test battery in combination with QOL and mood states measures in long-term adult survivors with a minimum survival of 2 years or more. However, it is preliminary and has some methodologic limitations. The sample size is relatively small due to the low survival rates and the limited number of disease-free survivors. Another limitation is that all patients in our study received a conditioning regimen with high-dose chemotherapy and TBI and the effects directed to TBI only were not assessed. In addition, with this sample size, we were unable to assess whether specific chemotherapeutic agents or dosages affect cognitive functioning. Similarly, the retrospective design and lack of pretreatment baseline assessment preclude definite conclusions about a change in cognitive functioning over time. The best way to evaluate the side effects of BMT treatment on cognitive functioning is through a longitudinal cohort study using a comprehensive neuropsychological test battery instead of a cognitive screening test or questionnaires only. Our results highlight the demand for systematic investigations on the late neurocognitive effects of BMT treatment in adult patients. We have started a prospective and longitudinal cross-sectional study to assess cognitive functioning and QOL.

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