available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

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

Helena Harder[a], *Arthur R. Van Gool*[b], *Hugo J. Duivenvoorden*[c], *Jan J. Cornelissen*[d], *Wil M.H. Eijkenboom*[e], *Renée M.Y. Barge*[f], *Martin J. van den Bent*[a,*]

[a]*Department of Neuro-Oncology, Erasmus Medical Center, Daniel den Hoed Cancer Center, P.O. Box 5201, 3008 AE Rotterdam, The Netherlands*
[b]*Department of Psychiatry, Erasmus Medical Center, Daniel den Hoed Cancer Center, Rotterdam, The Netherlands*
[c]*Department of Medical Psychology and Psychotherapy, Erasmus Medical Center, Rotterdam, The Netherlands*
[d]*Department of Haematology, Erasmus Medical Center, Daniel den Hoed Cancer Center, Rotterdam, The Netherlands*
[e]*Department of Radiotherapy, Erasmus Medical Center, Daniel den Hoed Cancer Center, Rotterdam, The Netherlands*
[f]*Department of Haematology, Leiden University Medical Center, Leiden, The Netherlands*

ARTICLE INFO

Article history:
Received 11 April 2007
Received in revised form 6 June 2007
Accepted 20 June 2007
Available online 23 August 2007

Keywords:
HSCT
Cognitive functions
Quality of life
Chemotherapy
TBI
Case-referent study

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

* *Corresponding author:* Tel.: +31 10 4391415; fax: +31 10 4391031.
E-mail address: m.vandenbent@erasmusmc.nl (M.J. van den Bent).
0959-8049/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2007.06.005

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