Clinical and quality of life responses to high-dose chemotherapy plus autologous stem cell transplantation in patients with multiple sclerosis: two case reports

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During the last several years high-dose chemotherapy (HDCT) with autologous stem cell transplantation (ASCT) has been established as a therapeutic option for multiple sclerosis (MS) patients. We report on the long-term effects of HDCT+ASCT in two female patients affected by secondary progressive and relapsing-remitting types of MS, respectively. As a result, disease stabilization was achieved in the first case and disease improvement in the second one. Both patients were off immunosuppressive or immunomodulating therapy throughout the post-transplant period. Notably, HDCT+ASCT resulted in an excellent quality of life (QoL) response in both cases. Our findings demonstrate that HDCT+ASCT could be considered as an effective treatment for MS patients. Moreover, QoL measurement seems to be an effective approach to assessment of treatment outcomes at long-term follow-up of patients with MS.

Keywords
autologous stem cell transplantation, high dose chemotherapy, multiple sclerosis, quality of life, quality of life response.

Introduction

BMT has contributed significantly to the treatment of life-threatening hematologic and non-hematologic disorders. Recently, high dose chemotherapy (HDCT) with autologous stem cell transplantation (ASCT) was proposed as a new and promising therapy for multiple sclerosis (MS) patients [1–5]. MS is a chronic inflammatory disorder of the central nervous system (CNS), caused by autoimmune reactivity of T cells towards CNS myelin components. Although MS is a non-life-threatening disorder, its progression inevitably leads to impairment of motor function, sensitive disturbances and cognitive impairment in MS patients because of the immune-mediated demyelination and axon degeneration [6]. The clinical course of the disease is very heterogeneous; however, most of the patients experience ‘relapsing–remitting’ disease initially, which is characterized by intermittent exacerbations followed by neurologic recovery. This disease stage is usually followed by gradual neurologic impairment, known as secondary progressive disease [7]. The neurologic disability in MS patients is quantified according to the expanded disability status scale (EDSS) [8]. The EDSS scores range from 0 (no disability) to 10 (death related to neurologic progression) in 0.5-step increments. EDSS scores from 1.0 to 4.5 refer to fully ambulatory MS patients, while patients with EDSS scores of 7.0 are essentially restricted to a wheelchair.

Conventional therapies do not provide satisfactory control of MS. Although results of pre-clinical studies suggest that allogeneic transplantation may lead to the decreased incidence of relapses of autoimmune disease, in a clinical situation the toxicity of allogeneic SCT results in an unacceptable rate of transplant-related morbidity and lethality. Therefore, HDCT+ASCT has been established...
as a therapeutic option for MS patients. However, the information about long-term effects of HDCT + ASCT in this patient population is scanty.

Another important consideration is selection of appropriate criteria for assessment of treatment outcomes for MS patients. Both disease-free period and improvement of patient's quality of life (QoL) are recognized as important outcome parameters. With this in mind, evaluation of both clinical and patient-reported outcomes in MS patients after HDCT + ASCT is worthwhile. However, neurologists traditionally only evaluate the clinical response and rarely use QoL data in the outcome analysis. This may be partly explained by the fact that QoL questionnaires used for MS patients, both generic and specific, are multidimensional, and interpretation of changes in several QoL scales/domains might be difficult for physicians. Recently, we have developed an approach to obtain an integral QoL index (IQLI) of profile questionnaires (both generic and specific ones). IQLI is a standardized value of the properties of a geometric profile formed by the scales of a questionnaire, and is assessed by the method of integral profiles [9]. The advantages of IQLI are its ease of use and the possibility of deriving one index from a basis of several QoL scales. The index has been validated [10]. The use of IQLI makes it possible to overcome difficulties in interpretation of QoL data and allows assessment of patient-reported outcomes, namely a QoL response.

According to our QoL treatment response concept the following grades of QoL response exist: minimal (less than 25% improvement compared with the baseline value), moderate (25–50% improvement), good (50–75% improvement) and excellent (more than 75% improvement). To date, limited information exists on the clinical response of MS patients receiving HDCT + ASCT at long-term follow-up, and data on QoL response are lacking.

Thus, reporting long-term effects of HDCT + ASCT in MS patients might give more grounds for HDCT + ASCT as a treatment option for this patient population.

**Case reports**

**Patient 1**

This patient, a 35-year-old female, was diagnosed with MS at the age of 28 in 1992 when she presented with progressive hypoesthesia of the right limbs and decreased color vision of the right eye. From 1992 to 1999, the patient developed progressive deterioration of neurologic function, decrease in motor functions and urinary retention. The patient was treated with steroids and plasmapheresis. There was no evidence of stabilization or improvement of the disease resulting from this treatment. The diagnosis of the secondary progressive type of MS was made in 1999. MRI examination before transplantation showed multiple widespread active lesions in the periventricular area. The EDSS score was 5.0.

The study was approved by the local IRB and ethical committee. Stem cells were mobilized with CY at 4 $g/m^2$, followed by G-CSF at 10 $\mu g/kg$. A Haemonetics MCS instrument (Haemonetics Corp., Braintree, MA, USA) was used for autologous stem cells aphaeresis. The BEAM conditioning regimen included BCNU (300 mg/m$^2$) on day $-6$, etoposide (200 mg/m$^2$) from day $-5$ to day $-2$ and cytarabine (200 mg/m$^2$) and melphalan (140 mg/m$^2$) on day $-1$. This was followed by autologous blood stem cell transplantation for rescue of hematopoietic and immune systems, and infusion of 30 mg/kg of horse ATG on days 1 and 2 for *in vivo* T-cell depletion. On day 0 the patient received $6.6 \times 10^6$ CD34$^+$ stem cells/kg. No life-threatening events were noted during transplantation. Post-transplant toxicity included neutropenia with a neutrophil count $<0.5 \times 10^9/L$ (from day $+2$ to day $+11$), anemia with a Hb concentration $<85 \ g/L$ (from day $+2$ to day $+11$), thrombocytopenia with a thrombocyte count $<50 \times 10^9/L$ (from day $+4$ to day $+24$), enteropathy (from day $+7$ to day $+11$), fever (from day $+5$ to day $+11$), esophageal candidiasis (from day $+10$ to day $+37$), bladder atonia (from day $+5$ to day $+21$), cystitis (from day $+10$ to day $+37$) and perianal tenderness (from day $+9$ to day $+14$).

Clinical and QoL assessments were provided at baseline, at discharge, then at 3 months, 6 months and every 6 months thereafter up to 48 months, and then at yearly intervals. Neurologic assessment included measuring the EDSS score and MRI examinations. QoL was assessed by the functional assessment of a cancer therapy–bone marrow transplant (FACT-BMT) questionnaire [11]. The FACT-BMT is a self-administered instrument designed to assess multidimensional aspects of QoL in BMT patients. It consists of a 27-item FACT general scale and a 23-item bone marrow transplantation subscale (BMTS). IQLI was calculated as described previously [10].

HDCT + ASCT appeared to have stabilized the disease and improved MRI findings. The EDSS score had dropped by 0.5 points (from 5.0 to 4.5) at 1.5 years post-transplant and remained stable throughout the time of follow-up. The
results of MRI scans 3 years after HDCT + ASCT revealed a decrease in the number of lesions and disappearance of edema around them. All lesions had turned to an inactive status. The MRI scans remained inactive at the end of follow-up. Significant QoL improvement was observed at 1 year after HDCT + ASCT. Further improvement of QoL parameters took place at long-term follow-up (Figure 1a). The IQLI increased dramatically from 0.16 at baseline to 0.70 at the end of follow-up. According to the grades of QoL improvement, by a year after transplantation more than 50% QoL improvement had taken place and by 2.5 years an excellent QoL response (more than 75% QoL improvement) was achieved. Further QoL assessment also revealed excellent QoL response at the end of follow-up.

Patient 2
The patient, a 21-year-old female, presented at the age of 19 in 1998 with myasthenia and unsteadiness. Diagnostic testing revealed MS. Despite therapy with steroids and plasmapheresis the patient developed progressive myasthenia, tremor of the right limbs and a decrease of motor functions. MRI examination revealed multiple widespread active lesions in the periventricular and subcortical area, white substance, brain stem and corpus callosum. The EDSS score was 4.0. The diagnosis of the relapsing–remitting type of MS was made in 1999. The patient was referred for HDCT + ASCT. The terms of transplantation were the same as reported for patient 1. On day 0 the patient received $5.4 \times 10^6$ CD34\(^+\) stem cells/kg. No life-threatening events were noted during transplantation. Post-transplant toxicity included neutropenia with a neutrophil count $< 0.5 \times 10^9$/L (from day + 4 to day + 12), anemia with a Hb concentration $< 80$ g/L (from day −1 to day + 33), thrombocytopenia with a thrombocyte count $< 50 \times 10^9$/L (from day + 4 to day + 28), enteropathy (from day + 5 to day + 13), fever (from day + 16 to day + 23) and esophageal candidiasis (from day + 5 to day + 30).

The terms of clinical and QoL assessment were the same as reported for patient 1. The patient received no treatment during the 5-year period post-HDCT + ASCT. As a result of HDCT + ASCT, disease improvement was registered. The EDSS score dropped by 0.5 points (from 4.0 to 3.5) by 3 months post-transplant and remained stable for 1.5 years, then dropped by 0.5 (from 3.5 to 3.0) and was stable throughout the rest of the time of follow-up. The results of an MRI scan 2 years after HDCT + ASCT revealed a decrease in the number of lesions in all areas. The MRI scans remained inactive at the end of follow-up. Significant QoL improvement was observed at 6 months after HDCT + ASCT. Further improvement of QoL parameters were measured at baseline and at different time points after HDCT + ASCT.

Figure 1. Quality of life profiles of MS patients 1 (a) and 2 (b). Values on radial axes correspond to FACT-BMT scales for physical functioning (physical F), social functioning (social F), emotional functioning (emotional F), everyday functioning (everyday F) and symptoms scale (symptoms). QoL parameters were measured at baseline and at different time points after HDCT + ASCT.
parameters took place at long-term follow-up (Figure 1b). The IQLI increased dramatically from 0.54 at baseline to 0.95 at the end of follow-up. According to the grades of QoL improvement, by 6 months after transplantation an excellent QoL response (more than 75% QoL improvement) was achieved. An excellent QoL response remained until the end of follow-up.

Discussion

It is important to emphasize that there are two goals to the treatment in MS patients. The first one is pathogenetic, which is to stop the disease progression and prevent the appearance of new lesions in the nervous tissue. The second, which is considered to be the final goal of a patient’s treatment, is to improve or maintain her or his QoL. Although some the recent studies have reported promising results of HDCT + ASCT for MS [1–5], analysis of long-term QoL outcomes in this patient population is lacking.

Therefore we investigated the long-term effects of HDCT + ASCT on the clinical course of disease and QoL of two MS patients. To our knowledge, these are the first case reports of both clinical and patient-reported outcomes for HDCT + ASCT in MS patients with long-term follow-up. Both patients were females (a 35-year-old woman and a 21-year-old woman) affected by the secondary progressive type and relapsing-remitting type of MS, respectively. As a result, disease stabilization was achieved in the first case, and disease improvement in the second. Both patients were off all therapy throughout the post-transplant period. Notably, both patients had a relatively low EDSS score, which may explain their good response to therapy.

Considering the pivotal role of autoreactive T cells in MS pathogenesis, their eradication has to be a primary objective of MS treatment. This is achieved through ablation of the patient’s immune system with HDCT. HDCT is followed by ASCT to restore an immune system that is expected to become tolerant to autoantigens. However, such ‘resetting’ of the immune system is only effective at early stages of MS, particularly in relapsing–remitting MS. Later in the clinical course of the disease, processes of axonal degeneration prevail and the damage to CNS tissue is too significant to expect a neurologic recovery after HDCT + ASCT. Indeed, failure of HDCT + ASCT to prevent progression of the disease when performed during late stages has been shown in both animal models [12] and in recent clinical studies [3,4]. Our findings corroborate these data, as the patients who benefited from HDCT + ASCT had a low disability score.

Notably, HDCT + ASCT resulted in an exceptional QoL response in both cases described in our study. The first patient achieved an excellent QoL response 2.5 years after transplantation. Surprisingly, the second patient experienced an excellent QoL response just 6 months after HDCT + ASCT. The well-being of the patients, namely their physical, psychologic and social functioning, improved dramatically: a more than 75% QoL improvement compared with the baseline. Complex evaluation of QoL parameters is a convenient way for assessing treatment outcomes in such a heterogeneous group as the MS patient population.

Finally, both cases demonstrated that HDCT + ASCT may be an effective treatment for MS in terms of clinical and patient-reported outcomes at long-term follow-up. Notably, QoL is a measurable outcome of HDCT + ASCT in patients with MS, and evaluation of the QoL response is highly recommended. Further studies should be done to investigate the long-term effects of HDCT + ASCT in MS patients for better definition of a treatment success.

References


