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Patient-reported outcomes in multiple sclerosis patients undergoing autologous stem cell transplantation

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Abstract

Physical, psychological, and social function in MS patients is significantly deteriorated. Quality of life profile of the patients is characterized by compression and deformation. The majority of the patients exhibit either severe or critical QoL impairment. MS patients experience a wide range of disease-related symptoms; the most frequent symptoms are fatigue, toddling, heat sensitivity, psychological problems (anxiety and sadness), and numbness/tingling are present in more than 70% of patients. About half of all patients report these symptoms at the moderate-to-severe level. ASCT in MS patients improves their physical, psychological, and social function. The most definite improvement of quality of life takes place within a year of transplantation. After ASCT the number of patients with no QoL impairment increases and the number of patients with critical QoL impairment decreases. Quality of life treatment response was achieved in the vast majority of MS patients after ASCT. ASCT is associated with decline of symptom prevalence and severity in MS patients.

Keywords: multiple sclerosis, autologous stem cell transplantation, ASCT, quality of life, symptoms

Introduction

Multiple sclerosis (MS) is a major inflammatory and demyelinating disease of the central nervous system (CNS), associated with a broad spectrum of physical, psychological, and social impairments. MS patients suffer from a variety of symptoms such as fatigue, spasticity, problems with balance and coordination, visual impairment, bowel or bladder dysfunction, decreased cognitive function, etc., and these symptoms decrease their quality of life (QoL) [6,11]. Most importantly, the level of impact of the wide range of health problems associated with MS needs to be understood in terms of patients' own perceptions of those impacts and the degree to which they affect their lives [9,4].

Currently there is no known cure for MS. Thus, the goal of treatment is to control symptoms and improve a patient's quality of life. In order to evaluate the efficacy of treatment or rehabilitation of MS patients it is necessary to assess patients' QoL and severity of symptoms [5,10]. "Quality of life of a patient" is a new and important category in clinical medicine. To assess it in a proper way it is worthwhile to define it clearly.

There are many definitions of QoL at present. The one which is most relevant to clinical setting is as follows: "Quality of life is integral characteristics of a physical, psychological,

and social functioning of an individual, based on his/her subjective perception" (A. Novik, T. Ionova, P. Kind, 1999).

This definition covers 3 major domains of an individual's function:
(1) Physical well-being;
(2) Psychological well-being;
(3) Social well-being.

Importantly it implies self-assessment. Special tools have been developed to measure QOL and symptoms. QoL questionnaires and symptom assessment tools refer to patient-reported outcomes (PRO) [2,1]. PRO is an umbrella term that is widely used at present. It covers a whole range of potential types of measurement, but is used specifically to refer to questionnaires completed by the patient. The most commonly used PRO measures assess QoL and symptoms.

There are several QoL measures which are used for evaluating QOL in MS. The most widespread are general QoL questionnaires: RAND Short Form-36 (SF-36), EQ-5D, and Sickness Impact Profile (SIP). MS-specific measures of QOL include the Functional Assessment of Multiple Sclerosis (FAMS), the Multiple Sclerosis Quality of Life-54 Instrument (MS-QOL-54), and the Disability & Impact Profile (DIP).

As for symptom assessment tools it is worth mentioning the Comprehensive Symptom Profile-MS-22 Short Form (CSP-MS-22-SF). This instrument was developed in 2007 by the New Jersey Center for Quality of Life and Health Outcome Research (USA) and Multinational Center for QoL Research (Russia) [3]. The CSP-MS-22-SF aims to assess the severity of 22 symptoms that are common and most disturbing for MS patients. It consists of numerical analogous scales, scored from "0" (no symptom) to "10" (most expressed symptom). Applicability of CSP-MS-22-SF with the analysis of its psychometric properties was tested in the study which included more than 120 patients with different types of MS.

At present high-dose immunosuppressive therapy with autologous hematopoietic stem cell transplantation (ASCT) has been used with increasing frequency as a therapeutic option for MS patients. Both disease-free period and improvement of the 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 ASCT is worthwhile. A comprehensive analysis of PRO has not been available. Thus, we aimed to study PRO in MS patients after ASCT.

Patients and methods

101 patients with MS (secondary progressive: 41 patients, primary progressive: 21, progressive-relapsing: 5 and relapsing-remitting: 34) were included in this study (mean age 32.5, range: 17–54; male/female 42/59). BEAM or BEAM-modified conditioning was used. Median EDSS at baseline was 5.0 (range 1.5–8.5). The mean follow-up duration was 21 months (range 6–120 months).

QoL was assessed using RAND SF-36 and FAMS. RAND SF-36 is a general QoL measure which consists of 36 questions and contains 8 scales: physical functioning, role–physical functioning, bodily pain, general health, vitality, social functioning, role–emotional functioning, and mental health. The FAMS is disease specific to assess QoL in MS patients. It consists of 58 questions and contains 7 scales: mobility, symptoms, emotional well-being, general contentment, thinking and fatigue, family/social well-being, additional concerns. Symptom severity was assessed using CSP-MS-22-SF. Patients filled in the questionnaires at baseline, at discharge, at 3, 6, 9, and 12 months, and every 6 months thereafter.

QoL treatment response was classified as improvement, stabilization, or worsening. To determine QoL treatment response the Integral QoL Index (IQLI) was calculated for each patient using the method of Integral Profiles on the basis of SF-36 scales (A. Novik, T. Ionova, A. Kishtovich, 2005) [8].

Using IQLI the grade of QoL impairment was determined for each patient. According to the grades of QoL impairment, five groups of patients can be identified: with no QoL impairment, mild QoL impairment, moderate QoL impairment, severe QoL impairment, and critical QoL impairment [7].

No QoL impairment means that a patient has no QoL decrease from a population norm (PN), mild QoL impairment <25% decrease from a PN, moderate QoL impairment 25–50% decrease from a PN, severe QoL impairment 50–75% decrease from a PN, and critical QoL impairment >75% decrease from a PN.

Results

Quality of life parameters in MS patients after ASCT

Monitoring of QoL parameters using the MS specific QoL questionnaire FAMS was made. QoL parameters at discharge, 6 months post-transplant, and 12 months post-transplant as compared to base-line are presented on Fig. 1–3. As can be seen from the figures, quality of life parameters are lower at the baseline than after ASCT across the majority of FAMS scales. Statistically significant improvement at baseline was found for the following scales: emotional well-being ($p<0.001$), general contentment ($p<0.05$), family/social well-being ($p<0.001$), and additional concerns ($p<0.001$).

In 6 months after ASCT statistically significant improvement as compared to base-line was registered across all scales except family/social well-being and additional concerns: mobility ($p<0.001$), symptoms ($p<0.001$), emotional well-being ($p<0.01$), general contentment ($p<0.01$), thinking and fatigue ($p<0.01$), and additional concerns ($p<0.001$). In a year the post-transplant QoL parameters had further increased with statistically significant improvement across all scales ($p<0.01$) except family/social well-being.

Mean total FAMS score at base-line was 115.5 (SD 29.6). At discharge it improved to 121.1 (SD 29.8; $p<0.05$) with further improvement in 6 months (mean 130.6; SD 31.8; $p<0.01$), and in a year post-transplant (mean 134.8; SD 28.1; $p<0.001$).

Further analysis included the comparison of QoL parameters

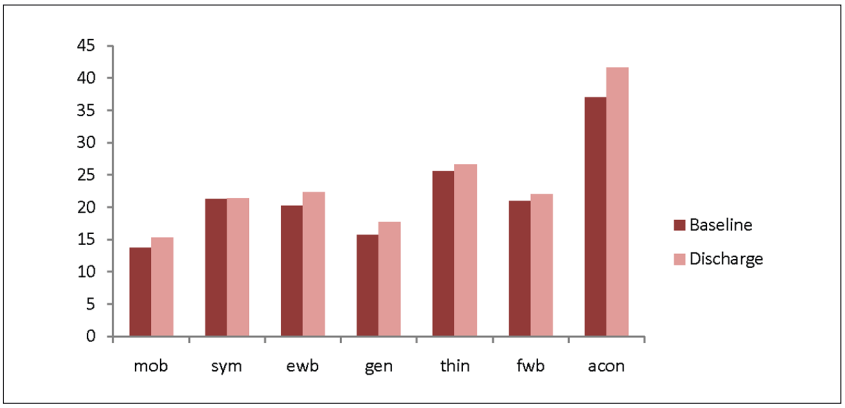


Figure 1. Quality of life parameters of MS patients before ASCT and at discharge (FAMS questionnaire)

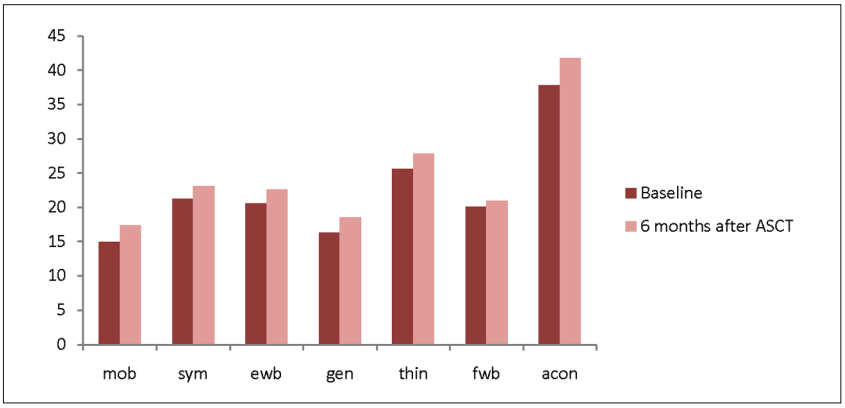


Figure 2. Quality of life parameters of MS patients before ASCT and 6 months after ASCT (FAMS questionnaire)

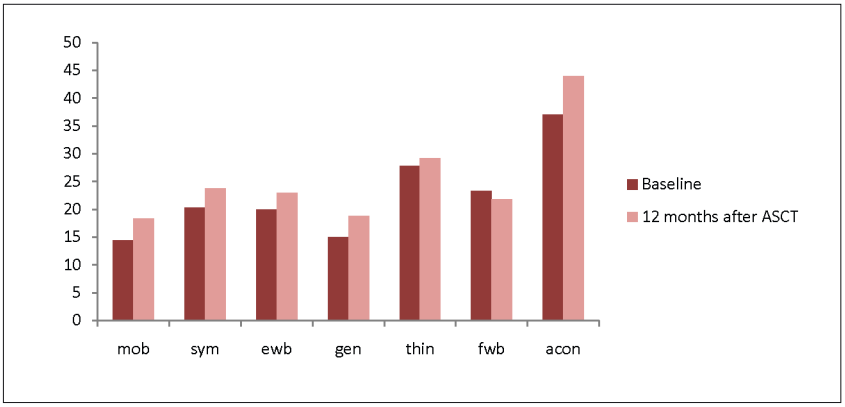
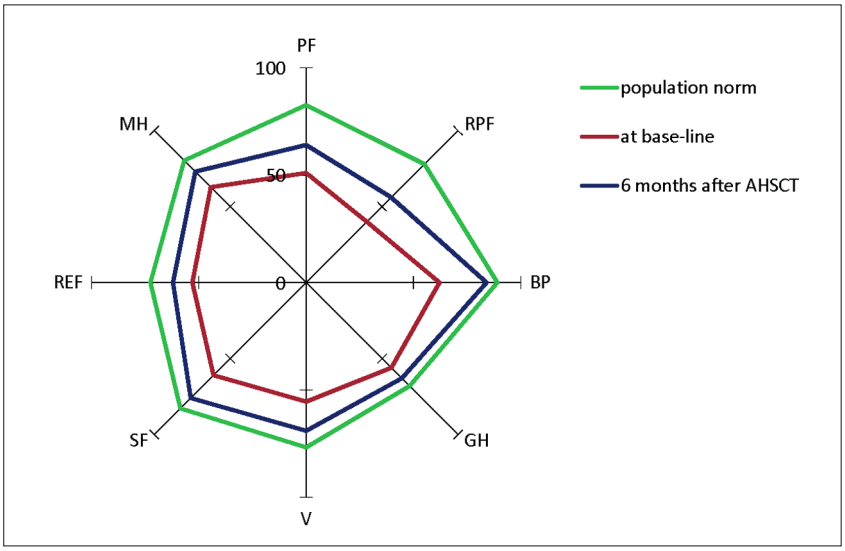


Figure 3. Quality of life parameters of MS patients before ASCT and 12 months after ASCT (FAMS questionnaire)



of MS patients before and after ASCT as compared with the population norm. For these purposes QoL was measured using RAND SF-36. Quality of life profiles of MS patients at baseline and 6 months post-transplant as well as of the population norm are presented in Fig. 4. As can be seen, the quality of life profile in MS patients before ASCT is characterized by compression and deformation as compared with the population norm. Quality of life parameters of MS patients before ASCT were significantly lower than of the population norm across all SF-36 scales. Six months after transplantation definite improvement of QoL parameters was registered, with statistically significant changes across all the scales ($p<0.01$) except pain and role–emotional functioning. The Mean Integral QoL Index increased dramatically as compared to base-line value (0.32 (SD 0.26) vs. 0.50 (SD 0.28); $p< 0.01$).

Taking into account the patients' heterogeneity in terms of their QoL the patients were stratified at baseline by the grades of QoL impairment. Five groups were identified according to the grades of QoL impairment: with no QoL impairment, mild QoL impairment, moderate QoL impairment, severe QoL impairment, and critical QoL impairment.

Distribution of patients according to the grades of QoL impairment before and 6 months after ASCT is shown in Table 1.

Changes in the distribution of patients according to the grades of QoL impairment took place after ASCT. The number of patients with no QoL impairment increased after transplantation, while the number of patients with critical QoL impairment decreased. Notably, ASCT resulted in a two-fold increase in the number of patients with QoL comparable to population norms: before transplantation 27% of patients had no QoL impairment, and 6 months after ASCT it was 52%. At the same time the number of patients with critical QoL impairment had experienced a triple decrease: at base-line 27% of patients had critical QoL impairment, and 6 months after ASCT it was only 6%.

Figure 4. Quality of life profiles in MS patients before and 6 months after ASCT as compared with the population norm (SF-36 questionnaire)
Note: PF = physical functioning, RPF = role–physical functioning, BP = bodily pain, GH = general health, V = vitality, SF = social functioning, REF = role–emotional functioning, MH = mental health.

QoL impairment grade	N, %	
	Before ASCT	After ASCT
No QoL impairment	9 (27)	17 (52)
Mild QoL impairment	4 (13)	3 (9)
Moderate QoL impairment	1 (3)	4 (13)
Severe QoL impairment	10 (30)	7 (20)
Critical QoL impairmen	9 (27)	2 (6)

Table 1. Distribution of patients according to the grades of QoL impairment before ASCT and 6 months post-transplant (n=33)

Thus, ASCT is accompanied by an increase in the number of patients with no QoL impairment and a decrease in the number of patients with critical QoL impairment.

Symptoms in MS patients after ASCT

Symptom prevalence in MS patients before and after ASCT is presented in Fig. 5. Before transplantation MS patients experienced a wide range of symptoms. The most prevalent symptom was fatigue (83%). Of those who had fatigue about half of the patients reported it at moderate-to-severe level. The other frequent symptoms were toddling, heat sensitivity, psychological problems (anxiety and sadness) and numbness/tingling with their prevalence of 79%, 76%, 72%, and 70%, respectively. More than half of the patients reported these symptoms at the moderate-to-severe level. The majority of patients (60% on average) experienced such symptoms as movement disorders, coordination problems, urination dysfunction, and vision impairment.

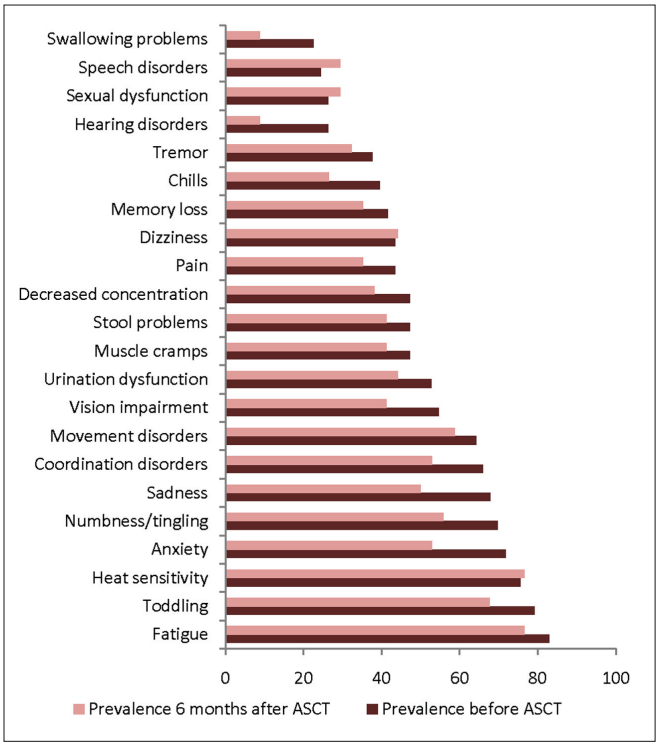


Figure 5. Symptom prevalence in MS patients before ASCT and 6 months post-transplant

Symptoms	Before ASCT	6 months after ASCT
	Mean (SD)	Meand (SD)
Toddling	5.3(4.1)	4.2(4.0)
Heat sensitivity	4.7(3.7)	4.5(3.8)
Fatigue	4.4(3.1)	3.5(3.0)
Movement disorders	3.9(3.8)	3.2(3.8)
Coordination disorders	3.7(3.8)	3.0(3.8)
Urination dysfunction	3.3(3.8)	1.9(2.8)
Numbness/tingling	3.3(3.3)	1.8(2.4)
Stool problems	3.2(3.6)	2.4(3.4)
Anxiety	3.0(2.9)	1.8(2.7)
Vision impairment	2.8(3.4)	1.9(3.1)
Sadness	2.8(3.0)	1.6(2.7)
Dizziness	2.3(2.9)	1.2(2.0)
Muscle cramps	2.1(3.0)	2.0(3.0)
Sexual dysfunction	2.0(3.7)	1.4(2.9)
Pain	1.5(2.2)	1.2(2.1)
Decreased concentration	1.3(1.9)	1.4(2.5)
Memory loss	1.1(2.0)	1.2(2.3)
Tremor	1.1(1.9)	0.9(2.0)
Chills	0.8(1.9)	1.3(2.7)
Speech disorders	0.7(1.9)	0.9(1.8)
Hearing disorders	0.5(1.7)	0.4(1.6)
Swallowing problems	0.4(0.8)	0.3(1.1)

Table 2. Symptom severity in MS patients before ASCT and 6 months post-transplant

In response to treatment, changes in symptom prevalence in MS patients were found. Positive changes in prevalence of the most frequent symptoms — fatigue, toddling, psychological problems (anxiety and sadness), numbness/tingling, movement disorders, coordination problems, urination dysfunction, and vision impairment — were observed 6 months after ASCT. The prevalence of the vast majority of moderate-to-severe symptoms after transplantation was lower than before treatment.

Information about symptom severity in MS patients before and 6 months after ASCT is presented in Table 2. Before transplantation the most severe symptom was toddling followed by heat sensitivity, fatigue, movement disorders, and coordination disorders. In response to treatment, the severity of these symptoms decreased. As it is seen from the table the mean value of the severity of these symptoms 6 months after ASCT was lower than before treatment. The severity of other symptoms decreased as well.

QoL treatment response in MS patients after ASCT

QoL treatment response characterizes changes in physical, psychological, and social functioning of a patient after treatment. Three types of QoL treatment response after ASCT can be identified: improvement, stabilization, and worsening.

QoL treatment response was determined at different time-points after ASCT. Here we present the data on QoL treatment response at 6 months post-transplant (n=33). Three types of QoL treatment response were registered: improvement, stabilization, or worsening. QoL improvement or QoL stabilization was shown in the vast majority of patients. QoL improvement was achieved in 16 (48.5%) patients; and QoL stabilization in other 16 patients. QoL worsening was noticed in one patient only.

Thus, the vast majority of patients (97%) experienced either QoL improvement or QoL stabilization in 6 months after ASCT.

Conclusions

1. Physical, psychological and social functioning in MS patients is significantly deteriorated. The quality of life profile of these patients is characterized by compression and deformation. The majority of patients exhibit either severe or critical QoL impairment.

2. MS patients experience a wide range of disease-related symptoms. The most frequent symptoms — fatigue, toddling, heat sensitivity, psychological problems (anxiety and sadness), and numbness/tingling — are present in more than 70% of patients. About a half of the patients report these symptoms at the moderate-to-severe level.

3. ASCT in MS patients improves their physical, psychological and social function. The most definite improvement of quality of life takes place in a year after transplantation.

4. After ASCT the number of patients with no QoL impairment increases whereas the number of patients with critical QoL impairment decreases.

5. Quality of life treatment response (QoL improvement or QoL stabilization) was achieved in the vast majority of MS patients after ASCT.

6. ASCT is associated with decline of symptom prevalence and severity in MS patients.

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Оценки, данные пациентами с рассеянным склерозом после аутологичной трансплантации стволовых кроветворных клеток

Татьяна И. Ионова, Денис А. Федоренко, Никита Е. Мочкин, Кира А. Курбатова, Андрей А. Новик

Резюме

Физическая, психологическая и социальная функции у больных рассеянным склерозом (РС) существеннно нарушены. Это находит отражение в значительном ухудшении качества жизни больных, и степень этого ухудшения вариирует от средней тяжести до критической. Среди большого количества патологических симптомов, сопровождающих течение РС, наиболее частыми, присутствующими у 70 % больных, являются слабость, трудности в ходьбе („ковыляющая“ походка), повышенная чувствительность к теплу, психологические проблемы (чувство тревоги и уныния), ощущение онемения или покалывания на различных участках поверхности тела. Около половины больных с такими симптомами определяют их тяжесть от среднего уровня и выше. Аутологичная трансплантация стволовых клеток (АТСК) больным РС улучшает их физические, психологические и социальные функции. Наиболее отчётливо улучшение качества жизни проявляется в течение первого года после трансплантации. В частности, повышалось количество больных без нарушений показателей качества жизни, а также уменьшение количества больных, имевших до АТСК критическое снижение показателей качества жизни. Качество жизни в целом было улучшено в результате АТСК у подавляющего количества больных РС как за счёт сужения спектра патологических симптомов, так и уменьшения их тяжести.

Ключевые слова: рассеяный склероз, аутологичная трансплантация стволовых клеток, АТСК, качество жизни, симптомы

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