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The feasibility of high dose chemotherapy with autologous stem cell transplantation for multiple sclerosis

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Abstract

The results of observing 23 patients with multiple sclerosis who received autologous hematopoietic stem cell transplantation are shown in this article. The risks of an auto-HSCT and its advantages compared with other therapy methods, and also an optimal choice for the therapy predictors are discussed. The results show progress of disease in most cases after 12–18 months.

Keywords: autologous hematopoietic stem cell transplantation (auto-HSCT), multiple sclerosis

Introduction

Multiple sclerosis (MS) is a chronic immune-mediated disease of the central nervous system, producing multifocal neurological symptoms caused by nerve demyelination and progressive neurodegeneration. The pathological hallmark of MS is multiple demyelinated plaques (sharply defined areas of demyelination) in the white matter and widely distributed areas of degeneration [7,10]. The core process in MS is inflammatory, with T cells and their mediators triggering myelin injury; additionally, oligodendrocyte/myelin damage is often mediated by autoantibody fixation with consequent complement activation. Therefore, multiple sclerosis is an autoimmune condition with a complex pathogenesis involving cellular and humoral immune response activation [3].

Presently in MS four types of neural tissue injury can be distinguished [9]. Two of them are caused by activation of cellular and humoral immune system compartments, and the others are characterized by degenerative changes in oligodendrocytes with primary or distal injury. These four types can occur at the different stages of MS. The present conception of MS pathogenesis encompasses two basic mechanisms — autoimmune inflammation and neurodegenerative changes [1,11].

Multiple studies and clinical observations showed the progressive decrease of brain tissue total volume in MS [4,12,15,16]. The beginning of the disease course is characterized by repeated episodes of inflammation with new contrast-accumulating T2 lesions revealed by MRI. However a considerable amount of recent data suggests the importance of degenerative changes at the earliest stages of the disease [4]. Today the pathogenesis of MS is considered to be a complex process with

the inflammatory component being only a part of the general process.

Even small T2 lesions can be associated with general atrophy, though within the clinical course brain atrophy is not always associated with high EDSS scores. Recently much attention has been given to focal atrophy at different stages of MS [2,5,13,14]. Apart from direct cell damage, the mechanism of inflammation can exert a protective effect. The immune cells recruited to the inflammatory foci produce growth factors, are able to delete myelin-associated molecules, and can have a suppressive phenotype. Therefore there are still some controversies in the inflammatory concept to be resolved.

Patients with MS receive treatment with Copaxone, Betaseron, Rebif-44, monoclonal antibodies, and cytostatics. In MS cases the most promising seems to be a complex therapy aimed at inflammatory process suppression and neuroprotection [6,8].

The aim of our study was to investigate the role of autologous HSCT in treatment of patients with MS as a complex treatment.

The first autologous hematopoietic stem cell transplantation (auto-HSCT) was performed in 2001. According to protocol, the patients were divided into two groups based on the rate of disease progression. The patients with fast progression of MS belong to the first group. In this group we consider a salvage high-dose chemotherapy with fludarabine-melphalan conditioning regimen and auto-HSCT. The patients with a stable disease course were included into the second group and received BEAM as a conditioning regimen.

Inclusion criteria

- Definitive MS (McDonald, 2005)
- Relapsing-remitting MS; second progressive MS and aggressive MS with severe relapses.
- Age 18–55 yrs.
- Duration of MS ≥1 year
- EDSS 0–6.5
- MRI within the 30 days period before auto-SCT
- Standard therapy methods proven to be ineffective
- The increase of EDSS 1.5 (EDSS 3.0–5.0) or 1 (EDSS ≥5.5)
- 2 relapses in the last 24 months or 1 relapse in the last 12 months on standard therapy.

The follow-up period varied from 2 months to 8 years.

- Median age 34.5 (22–52) yrs
- Sex distribution: male: 11 patients, median age 31.7 (22–41) yrs; female: 12 patients, median age 37 (26–52) yrs
- PPMS = 5 patients, SPMS = 12 patients, R-RMS = 6 patients
- Median period from debut of MS to auto-SCT: 6.8 yrs
- Median EDSS: 5.7 (1.5–7.5)BEAM: 17 patients, Flu-Mel: 6 patients
- Median of neutropenia duration: 12.7 days (BEAM: 12.6, Flu-Mel: 12.8 days).

To evaluate the therapy effects, clinical scales and immunological and radiological methods were used. We used the EDSS scale, MSFC clinical outcome measure, and a relapse evaluation test. The methods of immunological status evaluation included:

- detection of oligoclonal bands (OCB) in plasma and cerebrospinal fluid (CSF)
- light chain detection in plasma and CSF
- plasma and CSF T cell cytofluorometry (CD 3+CD19-; CD3+CD8+; CD3+CD4+; CD3+CD19+; CD3-CD19+; CD3-CD20+; CD3-CD(16+56); CD3+CD(16+56); CD3+HLA-DR+; CD3-HLA-DR+; CD3+HLA-DR-; CD4+CD25+; CB19+CB27+ phenotypes).

For CSN visualization the following MRI protocol was used:

- Routine protocol with contrast (Gd)
- T2 and T1 volume
- T1 and T2 lesion calculation
- Brain volume evaluation

Prior to auto-HSCT the patients received the following treatment: pulse therapy with steroids: 90%, beta-IFN: (Betaseron, Rebif, Avonex) 54%, mitoxantrone: 15%, Copaxone: 22%, intravenous IgG: 5%, no previous treatment: 5%.

Outcomes

Clinical symptoms evaluation: two end-points for EDSS assessment were established (day 0 and 12 months after auto-SCT). An evident therapy effect was observed in three patients, with decreases of EDSS scores from 6.5 to 1.5 in one patient, and from 5.5 to 4.5 in two patients. 10 patients (43.4%) remained with stable EDSS score values for 12 months after auto-SCT. 4 patients (17.3%) experienced disease progression (increase of EDSS). One patient died of sepsis.

MRI metrics examined included the number of Gd enhancing lesions, number of T2 lesions, total T2 lesion volume, and atrophy evaluation (decrease of total brain volume; changes in the third ventricle diameter; atrophy of corpus callosum). In the 18-month period after auto-SCT an increase in T2 lesion volumes was observed in 8% of cases, 20.4% of patients developed new T2 lesions, and 12% of patients had T1 contrast lesions. MRI signs of general brain atrophy were found in 95.6% of patients. We observed a certain discrepancy of MRI signs: while the volume of T2 lesions decreased and no signs of systemic inflammation were observed, the atrophic changes continued to progress. Judging by MRI metrics, auto-SCT can eliminate the inflammatory, but not the neurodegenerative component of MS.

Immunology: We performed cytofluorometry of serum and CSF immunocompetent cell populations, and evaluated the level of intrathecal IgG as a highly specific marker of MS. Cell population changes showed no definite pattern and are hard to interpret. No evident dynamics of intrathecal IgG level was observed.

After ASCT 91.1% patients had constant intratecal synthesis

of OCB. Only in 1 patient we revealed no signs of OCB synthesis in CSF and plasma.

Early post-transplant period complications: infectious complications: 84%; hemorrhagic complications: 54%; serum sickness: 44%; neurological complications: 30%.

Conclusions

Our results show the evident decrease of inflammatory changes and better disease control in MS patients treated with conventional chemotherapy or high-dose chemotherapy with auto-HSCT due to its immunosuppressive effect. However, more intensive therapy is associated with a higher complications rate and risk of mortality. There are some questions still unanswered. It is still to be determined whether the conventional regimens able to roll the disease course back to previous stages or more radical high-dose therapy lead to better long-term survival and disease control. Also still to be determined is the best time for high-dose therapeutic intervention.

On the whole, auto-HSCT is a promising method of MS treatment, but there are certain practical aspects to be developed:

- Indications for auto-SCT
- Conditioning regimen
- Stem cell source and transplant processing
- Complex methods of disease course evaluation (clinical, immunological, radiological, and morphological evaluation)
- Quality of life evaluation
- Role of mesenchymal stem cells and monoclonal antibodies in the treatment of multiple sclerosis.

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Возможности АТСК при РС

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Резюме

В данной статье приводятся результаты наблюдения за 23 пациентами с рассеянным склерозом после проведенной аутологичной трансплантации стволовых кроветворных клеток. Обсуждаются риски высокодозной химиотерапии и ее преимущества перед другими методами терапии, а также оптимальный выбор режима кондиционирования и предикторов терапии. Результаты показывают прогрессирование заболевание у большинства пациентов после проведенной терапии через 12-18 месяцев.

Ключевые слова: аутологичная трансплантация стволовых кроветворных клеток (АТСК), рассеянный склероз

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