ABSTRACT

Multiple sclerosis (MS) represents a demyelinating disease of the central nervous system with known autoimmune etiology. Currently new diagnostic criteria are used allowing us to diagnose MS early after first relapse of clinical symptoms. Several drugs are available to reduce disease activity and postpone later MS stages with irreversible disability. Prognosis of an individual patient and accurate treatment is however defined only imperfectly based on our clinical experience and brain magnetic resonance imaging. Specific prognostic markers are missing.

Aims: 1. To identify suitable prognostic immunological marker from peripheral blood of MS patients in different disease stages and under different treatment regimens; 2. To describe group of MS patients treated with autologous stem cells transplantation (ASCT) or allogeneic stem cells transplantation (alloSCT) with respect to efficacy, adverse events and accurate patient selection.

Patients and methods: In the first part of the study we involved 33 patients with clinically isolated syndrome, 17 MS patients treated with natalizumab and 14 patients with aggressive MS treated with ASCT. Disability measured by Expanded Disability Status Scale (EDSS) as well as relapse rate were evaluated before treatment (baseline) and after 3, 6, 12 and 24 months after treatment initiation. In the same time-points peripheral blood was drawn and basic lymphocyte subpopulations and intracellular cytokines were examined using flow cytometry. T-test, ANOVA and multiple regression analysis were used for statistical analysis. In the second part of the study we collected clinical data (EDSS, relapse-rate, long-term MS treatment, adverse events) of 26 MS patients treated with ASCT (during period 1998-2008). We described two case-reports of alloSCT treatment as well (in MS and other demyelinating CNS disorder – neuromyelitis optica (NMO)). For statistical analysis Kaplan-Meier curve with progression free survival (PFS) calculation was used together with comparison of PFS of selected patient subgroups using Cox F test.

Results: Two-year follow-up of peripheral blood lymphocyte subpopulations in all three groups of patients (percentage (%) and absolute (abs) values) was described. Inter-group analysis showed significant difference in CD19+abs lymphocyte count at baseline between progressors and non-progressors measured by EDSS at month 24 ($p=0.01$). Threshold of 0.2 in CD19+abs lymphocyte count at baseline distinguished progressors and non-progressors with sensitivity 81% and specifity 46%. Predictive potential was statistically even more significant combining baseline CD19+abs lymphocytes and CD3+% lymphocytes at month 3 ($p<0.001$).

In the second part, at 3 and 6 years of follow-up 70.8% and 29.2% of patients treated with ASCT respectively were free of progression. Within three-year follow-up PFS was 84.4% in relapsing-remitting patients and 60% in secondary-progressive patients ($p=0.00002$). In the group of patients with MS duration < 5 years PFS achieved 82.3% in comparison with 61.8% in patients with MS duration ≥ 5 years ($p=0.00217$). There was also statistically significant difference between PFS in patients under age of 35 and older patients ($p=0.01118$). Treatment related mortality was 0% and ASCT procedure was relatively safe. Also alloSCT treatment was well-tolerated and effective in both patients with demyelinating CNS disorder.

Conclusion: Possible predictive marker of disability progression in MS was found in this study – absolute CD19+ B-lymphocyte count in peripheral blood. This work has shown that further research of basic immunological markers in peripheral blood is advisable in connection to MS prediction. In this work selection criteria for ASCT treatment were defined

and treatment was evaluated as relatively safe. AlloSCT treatment showed possible efficacy in autoimmune diseases of the CNS including NMO with known poor prognosis. In our two patients even this treatment was well-tolerated.