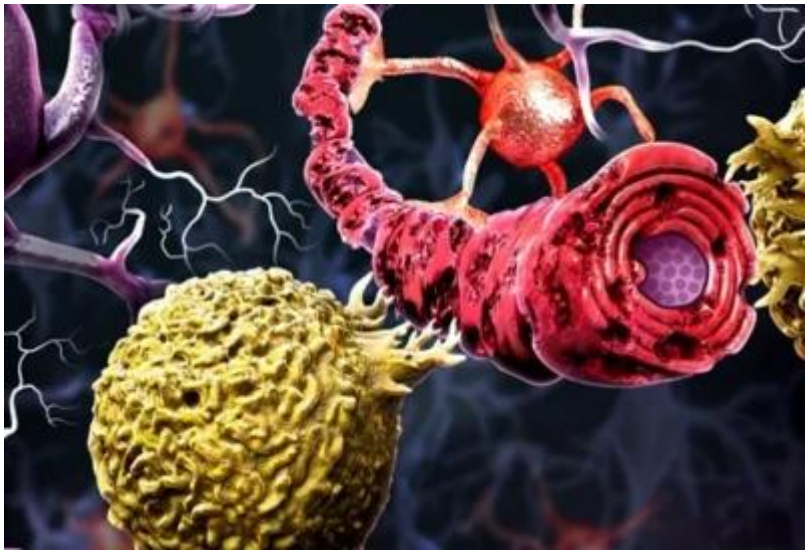
Multiple sclerosis (MS) is a chronic, immune-mediated, demyelinating disease of the central nervous system (CNS) that is caused by a multifactorial interaction of genetic and environmental factors. The majority of patients diagnosed with relapsing-remitting MS are successfully treated with disease-modifying therapies. However, some patients may develop a more aggressive course of disease refractory to such therapies. Since 1995, MS patients have been treated with autologous hematopoietic stem cell transplantation (AHSCT) to eliminate autoreactive immune cells with high-dose chemotherapy, followed by immune reconstitution after AHSCT. In this nationwide retrospective single-center study, Danish authors reported the results of AHSCT performed in 32 patients with relapsing-remitting MS.

MS is characterized by multiple areas of inflammation and demyelination in the white matter of the brain and spinal cord. The clinician manifestations are protean, determined by the various locations and extent of the demyelinating foci. MS plaques are demyelinating lesions of the CNS, characterized by infiltration of mononuclear cells, the proliferation of macrophages, and loss of oligodendrocytes, myelin-producing cells.

Two conditioning protocols are commonly used for AHSCT, the myeloablative BEAM regimen with carmustine, etoposide, cytarabine arabinoside, melphalan, and antithymocyteglobulin (ATG), and the non-myeloablative CY/ATG regimen with cyclophosphamide (CY) and ATG. According to the European Group for Blood and Marrow Transplantation (EMBT) 2020 guidelines, there is no evidence of a difference in efficacy or safety between the two regimens. Therefore, both types of AHSCT regimens are now recommended for patients with MS. A retrospective evaluation of AHSCT demonstrated a poor response in patients with chronic progressive MS and a better response in younger patients with aggressive relapsing disease.



About the study

This is a retrospective observational study of all Danish patients treated with AHSCT at a single institution. The inclusion criteria for treatment were: (1) diagnosis of aggressive relapsing-remitting MS, defined as either (a) severe disabling relapses and extensive magnetic resonance imaging (MRI) activity in untreated patients, (b) at least two severe, documented relapses and typical MRI activity in patients treated with the first-line treatment, or (c) one documented severe relapse and typical MRI activity in patients treated with the second-line treatment; (2) age 18–50 years, and (3) an Expanded Disability Status Scale (EDSS) score between 3.0-6.0.

For treatment were not eligible patients with progressive MS, Eastern Cooperative Oncology Group performance status score >2, pulmonary function test with forced expired volume in the first second or diffusion capacity below 40% of expected, and heart failure with left ventricular ejection fraction under 45%.

Patients underwent hematological and neurological follow-up for the first three months after AHSCT and at 6, 12, 18, and 24 months.

The adverse events (AEs) included toxicities from the chemotherapy, side effects from prophylactic treatment, infections, and other events during admission that the patient had never had before.

From May 2011 to May 2021, 32 patients underwent autologous hematopoietic stem cell transplantation. Seven patients underwent AHSCT with carmustine, etoposide, cytarabine

arabinoside, melphalan, and ATG regimen (BEAM/ATG), with a median follow-up of 49 months. Twenty-five patients underwent AHSCT with cyclophosphamide and ATG regimen (CY/ATG), with a median follow-up of 39 months. The two groups of patients had significant differences regarding age, disease duration, baseline EDSS, and relapse rate one year before AHSCT.

Results

Across the cohort, relapse-free survival was 77%, worsening-free survival was 79%, MRI event-free survival was 93%, and no evidence of disease (NEDA-3) was 69% at the end of the second year after the AHSCT. There was no treatment-related mortality.

The CY group had significantly higher two-year relapse-free survival (83%) compared to the BEAM group (57%), and significantly higher two-year worsening-free survival (85%) compared to the BEAM group (57%). The significant differences in relapse-free survival, worsening-free survival, and NEDA-3 between groups became insignificant after adjusting for sex, age, disease duration, baseline EDSS, and relapse rate one year before AHSCT.

The most common AEs reported during conditioning and the days after admission were nausea and vomiting, diarrhea, dyspepsia or reflux, abdominal pain, obstipation, mucositis, thrombocytopenia, anemia, neutropenic fever, infections, fatigue, fever, headache, and neurogenic bladder. After a discharge, the most common AEs were various infections that required hospitalization. Other relevant AEs after discharge included thyroid diseases and neoplasia. 14% of BEAM and 28% of CY patients developed thyroid diseases after AHSCT. 14% of BEAM patients developed cervical dysplasia five years after AHSCT, and 5% of CY patients developed a prolactinoma or a meningioma two years after AHSCT. There was no evidence of treatment-related mortality. One patient who was treated died six years after AHSCT.

Conclusion

This study has shown that AHSCT was a relatively safe and effective treatment for patients with aggressive relapsing-remitting MS included in the study. There were few serious AEs and no deaths. The less aggressive non-myeloablative CY/ATG regimen was as effective as the myeloablative BEAM/ATG regimen, with fewer adverse events.

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