Autologous haematopoietic stem cell transplantation affects leptomeningeal enhancement in multiple sclerosis: a longitudinal study

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Background and Objective

Leptomeningeal enhancement (LME) is considered a magnetic resonance imaging (MRI) marker of leptomeningeal inflammation in multiple sclerosis (MS), likely representing follicle-like structures constituted by chronic inflammatory infiltrates [1]. To our knowledge, available disease-modifying treatments do not substantially affect LME number in MS, possibly due to their poor blood-brain-barrier (BBB) penetration. Conversely, high-dose chemotherapy drugs bioavailable within the Central Nervous System (CNS) are administered during autologous haematopoietic stem cell transplantation (AHSCT), a haematological procedure endorsed as a standard of care for the treatment of aggressive relapsing MS [2]. In a previous pilot study from our group, LME number was reduced after AHSCT in 1/3 (33%) MS patients with LME at baseline [3]. In this study, the effect of AHSCT on LME persistence and formation was further explored in a prospective cohort of MS patients undergoing AHSCT at our centre.

Materials and Methods

Consecutive MS patients who received AHSCT in Florence in the period 2020-2023, and who performed a longitudinal MRI follow-up at predefined timepoints (before, at months 6-12 after AHSCT, and then yearly). The AHSCT protocol was the same in all the patients: haematopoietic stem cells were mobilized with cyclophosphamide (4 gr/m²); the conditioning protocol used was the intermediate-intensity regimen BEAM/ATG. Brain MRI scans were acquired on the same 3T machine (Ingenia, Philips) with a standardized protocol, including gadolinium-enhanced 3-dimensional fluid-attenuated inversion recovery (3D-FLAIR) sequences. LME foci were identified in co-registered 3D-FLAIR and gadolinium-enhanced T1 weighted MRI sequences by two independent raters blind to clinical data and MRI timepoints.

Results

Twelve MS patients were included. Baseline characteristics are summarized in table 1. The latest MRI timepoint was taken 6 months, 1 year and 2 years after AHSCT for 2, 9 and 1 patients, respectively. There were 11/12 (92%) females, 5 relapsing-remitting (RR-) and 7 secondary-progressive (SP-)MS. Median age and expanded disability status scale (EDSS) score at baseline were 42 (28-48) and 4.25 (1.5-6.5), respectively. In the baseline (i.e., pre-treatment) scan, 7/12 patients (58%) showed at least one LME, being the median number of LME foci 1 (range 0-4). Following AHSCT, no formation of new LME foci was observed. One LME disappeared in 2/7 patients (29%, both SP-MS) at the six- and 24-month follow-up, respectively. EDSS stabilized in both these patients at the same timepoints.

Table 1. Baseline characteristics of the MS patients included (n=12)

	Median (range)
Age, years	42 (28-48)
Disease duration (years)	11.5 (5-23)
Previous DMTs, number	3 (1-6)
EDSS	4.25 (1.5-6.5)
	n (%)
Sex, female	11/12 (92%)
MS form, RR	5/12 (32%)

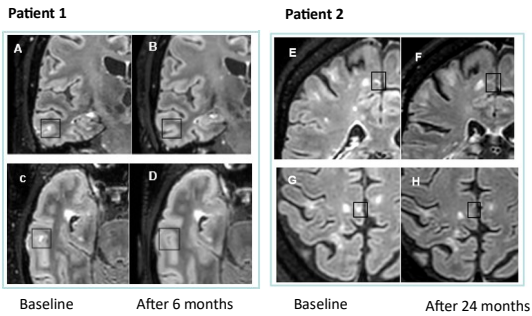

Figure 1. Examples of disappearance of LME foci in two patients over follow- up after AHSCT compared to the pre-treatment scan.

Disappearance of one LME focus detected on post Gd coronal (A and B) and axial (C and D) FLAIR scans at the 6th month timepoint.

Disappearance of one LME focus detected on post Gd coronal (E and F) and axial (G and H) FLAIR scans at the 24th month timepoint.

Discussion and Conclusion

This study suggests that AHSCT may affect the development and persistence of LME, confirming previous exploratory findings from our group. Such observation supports the hypothesis that chemotherapy administered during AHSCT can effectively reach the CNS compartment and affect compartmentalized inflammation. These preliminary findings also strengthen the indication for timely treatment of MS patients with therapies bioavailable within the CNS, and therefore potentially targeting compartmentalized inflammation, a putative key inflammatory driver of progression independent of relapse activity. In this context, further studies are needed to ascertain whether LME could represent a biomarker of treatment response.

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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