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Brief Report

European experience of cladribine tablets in elderly patients with multiple sclerosis: Could it be the last treatment?

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Abstract

Background: Recent studies support the need for early and intensive disease-modifying treatment (DMT) for patients with multiple sclerosis (PWMS). Abrupt DMT withdrawal may risk disease reactivation. Recent studies showed that MS disease activity was not rare after DMT withdrawal for PWMS aged >45/55 y. Immune reconstitution therapy (IRT) with cladribine tablets (CladT), may be an option for older PWMS who wish to stop DMT.

Objective: We retrospectively analysed PWMS aged >45 y who initiated CladT in 6 MS centers in Europe.

Results: One hundred and twenty nine PWMS (95 women/34 men, mean age 55.0 +/-7.5y initiated CladT; 83 (64.3%) previously received platform DMT, 35 (27.2%) previously received high efficacy DMT and 11 (8.5%) received CladT as a 1st DMT due to a late onset of MS or to a delayed therapy decision. Mean follow-up was 2.4 y (1–5) on CladT. Only three patient experienced 4 relapses. The first one had 2 relapses after switching from fingolimod with a 2-month interval between treatments. The 2 remaining were naïve patients that had a relapse between the 2 courses of CladT.

Conclusion: Last/exit therapy with CladT seems to avoid MS disease reactivation in older PWMS and may be an interesting alternative solution to continue immunosuppression/immunomodulation.

Keywords: multiple sclerosis, cladribine, exit therapy

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Introduction

Recent clinical studies support the need for early and intensive disease-modifying treatment (DMT) for patients with multiple sclerosis (PWMS).[1,2] However, a lot of patients are still receiving DMT even after 50–60 years of age. Abrupt DMT withdrawal may increase the risk of disease reactivation. Recent studies showed that MS disease activity was not rare after DMT withdrawal in PWMS aged >45–55 years.[3–7] This risk is estimated to be around 10% to 25% in patients with platform therapies (PLT),[3,4] but increase to at least 30–40% in patients treated with high efficacy treatments (HET) and especially with lymphocyte sequestration drugs such as sphingosine 1 phosphate (S1P) inhibitors and natalizumab.[5] Some dramatic rebound effects have also been reported after withdrawal of the latter types of HET.[6,7]

Immune reconstitution therapy (IRT) with cladribine tablets (CladT) can provide suppression of MS disease activity and is usually well tolerated. It could therefore represent an option for older PWMS who wish to stop DMT, the aim being 1) to avoid a reactivation or rebound of the disease; 2) to avoid the need for continuous immunosuppression.

The aim of this study was to report on the evolution of the disease in a cohort of European PWMS aged over 45 years at the time of treatment with CladT.

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Methods

We retrospectively analyzed all PWMS aged >45 years who initiated CladT before the end of 2023 in 6 European MS centers. Inclusion criteria were relapsing remitting patients older than 45 years-old with a stabilized disease on both inflammatory (clinical and MRI) and progression parameters encompassing non evidence of disease activity (NEDA) criteria. A few number of patients had a relatively high EDSS score (5.5–6.5) but were still considered on a relapsing remitting phase by the clinician and were included as they were stable from the 2 previous years without progression. Patients' clinical parameters analyzed were: age, sex, disease duration, last treatment used before CladT (if any), time duration between stopping the last treatment and CladT, retreatment with CladT, or switch to another treatment during the follow-up period. We analyzed the occurrence of a relapse, Expanded Disability Status Scale (EDSS) score at baseline, during the treatment, and at last follow-up. Disease progression was defined as an EDSS worsening of at least 1 point for patients with an EDSS score <5.5 and at least 0.5 points in patients with an EDSS score ≥5.5. MRI data were evaluated 3–6 months after CladT initiation (MRI rebaseline) and annually during the follow-up.

Results (table)

129 PWMS (95 women/34 men; mean age, 55.0 ± 7.5 years) initiated CladT; 83 (64.3%) had previously received PLT (interferon beta n = 19, teriflunomide n = 37, dimethyl fumarate n = 8, glatiramer acetate n = 19), 35 (27.2%) had previously received HET (S1P inhibitors n = 17, monoclonal anti-CD20 antibodies n = 12, natalizumab n = 5, alemtuzumab n = 1), and 11 (8.5%) received CladT as a first DMT in the context of late onset MS.

The prior HET and PLT groups were similar in terms of mean age (54.9 ± 7.9 years and 55.4 ± 7.4 years, respectively, p = 0.77), mean MS disease duration (18.6 ± 9.1 years and 17.8 ± 8.0 years, respectively, p = 0.66), and median EDSS score at CladT initiation (3.5 [range 2.0–6.0]) and 2.5 [range 2.0–4.0]) respectively, p = 0.08). Patients who initiated CladT as the first DMT had a similar mean age at baseline (52.3 ± 7.4 years, p = 0.18) compared with other groups but had a shorter mean disease duration (6.0 ± 11.2 years, p < 0.001) and a lower median EDSS score (2.25 [range 2.0–3.38], p = 0.03) (see Table 1). The mean time between the end of the previous treatment and CladT was 24 ± 7.1 days for all DMT excepted anti-CD20 and Alemtuzumab. For anti CD20 the interval was 9.2 ± 3.5 months and for the only patient previously treated with Alemtuzumab the interval was 3.4 years.

Mean follow-up on CladT was 2.42 ± 1.5 years. During this period, three patients experienced a total of four relapses: one patient had two relapses after switching from fingolimod with a two-month wash-out period and the other two were prior treatment-naive patients that had a relapse between the two courses of CladT.

MRI data showed reactivation on rebaseline MRI at month 6 (new T2 lesions) in three patients only, one that switched from fingolimod (the same patient that experienced two relapses) and 2 prior treatment-naive patients during the first year of the disease.

Eleven patients (8.5%) had EDSS progression (all without relapses). Four of the patients have previously been treated with anti-CD20 and had a median baseline EDSS score of 6.0, suggesting a progressive phenotype at CladT initiation.

Seven PWMS received additional treatment following the 2 courses of CladT: four received a further course of CladT (two due to MRI reactivation; two due to EDSS progression), two received ofatumumab (EDSS progression and MS relapse, respectively), and one received siponimod (EDSS progression).

Discussion

Our case series demonstrates a very good response to CladT, used as an exit therapy, in PWMS older than 45 years. This strategy seems to protect from any inflammatory reactivation of the disease whatever the type of prior treatment (PLT or HET). The only three patients with disease reactivation were two naive patient during the first year of CladT treatment and one patient who switched from fingolimod with a two-month interval. The two naive patients did not have any clinical relapses and continued the treatment.

Some patients (9.3%) had disability progression. These patients had a mean baseline EDSS score of 5.04 compared to a mean score of 2.01 in the remainder of the study population, which suggests that they may already have had a silent MS progression at CladT initiation. This is in line with studies showing that immune reconstitution strategies such as alemtuzumab or blood and marrow transplantation are not the best treatment option for secondary progressive forms of MS.[8,9]

Table 1. Demographical and clinical data from MS patients treated with cladribine as an exit therapy.

Treatment Type	No. of Patients	Sex Ratio (%W)	Mean (SD) Age at CladT Initiation, y	Mean (SD) Disease Duration, y	Median [IQR] EDSS score	No. (%) of patients with disease reactivations on CladT (Clinical and/or MRI)	No. (%) of Patients with Disease Progression
INF	N = 19	43%	56.6 (6.67)	18.4 (5.29)	2.5 [2.0; 3.75]	0 (0%)	1 (5.2%)
GA	N = 19	78.9%	53.6 (7.43)	14.8 (7.86)	2.50 [1.0; 5.5]	0 (0%)	3 (15.7%)
TER	N = 37	78.6%	56.3 (7.84)	19.6 (9.33)	3.0 [2.0; 4.0]	0 (0%)	0 (0%)
DMF	N = 8	66.6%	52.8 (6.11)	15.4 (5.58)	2.5 [2.0; 3.0]	0 (0%)	1 (0%)
TOTAL PLT	**N = 83**	**65.1%**	**55.4 (7.35)**	**17.8 (8.03)**	**2.5 [2.0; 4.0]**	**0 (0%)**	**5 (6.0%)**
S1Pi	N = 17	82.4%	56.4 (8.54)	19.0 (8.10)	2.5 [2.0; 4.75]	1 (5.9%) clinical and MRI	2 (11.8%)
Anti-CD20	N = 12	66.6%	53.7 (7.76)	18.4 (11.7)	6.0 [5.25; 6.62]	0 (0%)	4 (33.3%)
NTZ	N = 5	100%	53.8 (7.68)	16.6 (6.75)	2.0 [2.0; 2.5]	0 (0%)	0 (0%)
ALE	N = 1	0%	52	21.9	4	0 (0%)	0 (0%)
TOTAL HET	**N = 35**	**80%**	**54.9 (7.91)**	**18.6 (9.13)**	**3.5 [2.0; 6.0]**	**1 (2.8%)**	**6 (17.1%)**
CladT as first DMT	N = 11	72.7%	52.3 (7.39)	6.01 (11.2)	2.25 [2.0; 3.38]	2 (18.2%) MRI only	1 (9.0%)
All treatments	**N = 129**	**73.6%**	**55.0** (7.49)	**17.0** (9.21)	**2.5 [2.0; 4.75]**	**3 (2.3%)**	**11/129 (8.5%)**

Abbreviations: INF: interferon; GA: glatiramer acetate; TER: teriflunomide; DMF: dymethyl fumarate; S1Pi: sphingosine 1 phosphate inhibitor; NTZ: natalizumab; ALE: alemtuzumab; CladT: cladribine tablets; N: number; IQR: interquartile range; SD: standard deviation; W: women; EDSS: Expanded Disability Status Scale.

We suggest to check about silent progression or progression independent of any relapse activity (PIRA) before switching to CladT especially in patients with higher EDSS score. These patients should be more candidate to new therapeutical strategies more focused on focal inflammation such as Bruton kinase inhibitors.

Conclusion

Exit or last therapy with CladT seems to avoid MS disease reactivation in older PWMS irrespective of prior PLT, HET, or no DMT. A longer follow-up will determine whether these patients will need to be retreated in subsequent years. Although we observed only 1 rebound in a patient who switched from an S1P inhibitor, patients treated with lymphocyte sequestration and retention strategies (S1P and natalizumab) require special attention and should be switched with a short interval between treatments (≤1 month, as opposed to after 2 months in our case).

Conflict of interest statement

Prof Jerome de Seze received lecturing fees and travel grants from Biogen, Merck, Novartis, Roche, Alexion, Amgen, CSL Behring, UCB, LFB, Argenx, Sando, Pfeizer and Sanofi.

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Data availability statement

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Ethical statement

The EDMUS database was declared to the ethic comitee.

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Informed consent/ patient consent

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