

Safety and Tolerability of Subcutaneous Cladribine Therapy in Progressive Multiple Sclerosis

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ABSTRACT: *Objective:* To evaluate the safety and tolerability of subcutaneous (s.c.) cladribine therapy in patients with chronic progressive multiple sclerosis (CPMS), and to evaluate the effects on lymphocyte subsets. *Background:* Cladribine, a synthetic antineoplastic agent with immunosuppressive effects, may favourably affect the course of CPMS. However results of a previous reported clinical trial showed significant myelosuppression in some patients. *Design/Methods:* 19 patients with severe (mean extended disability status score [EDSS] = 6.7) CPMS were treated on a compassionate basis with cladribine 0.07 mg/kg/ day s.c. for 5 days per cycle, repeated every 4 weeks for a total of 6 cycles. Patients underwent clinical evaluation, EDSS, and hematologic analysis before, during, and following therapy. *Results:* The treatment was very well tolerated with no clinically significant side effects observed. Between baseline and the end of cycle 6, mean decreases were noted in absolute lymphocyte count from 1697 to 463 ($p = 0.000012$), CD4 count from 865 to 187 ($p = 0.0000008$), CD8 from 418 to 165 ($p = 0.005$) and CD19 from 197 to 26 ($p = 0.000002$). Platelet, granulocyte and RBC counts were unaffected. Approximately one year after completion of therapy, some recovery of CD4 and CD8 counts had occurred although both counts remained suppressed compared to baseline (302 and 227 respectively); the CD19 count had recovered essentially to normal by one year. EDSS scores post-therapy revealed some deterioration in 8 patients and stable scores in the remaining 11. Global patient evaluations of the treatment were mixed. *Conclusions:* Cladribine therapy, at lower doses than previously reported, was remarkably well tolerated in CPMS, with no significant myelosuppression. Profound effects occurred in total lymphocyte count and CD4, CD8 and CD19 subsets.

RÉSUMÉ: *Sécurité et tolérabilité de la cladribine sous-cutanée dans le traitement de la sclérose en plaques progressive.* *But:* D'évaluer la sécurité et la tolérabilité de la cladribine sous-cutanée (s.c.) chez les patients atteints de sclérose en plaques progressive chronique (SEPPC) et d'évaluer ses effets sur différentes populations lymphocytaires. *Introduction:* La cladribine, un agent antinéoplasique synthétique qui a des propriétés immunosuppressives peut influencer favorablement l'évolution de la SEPPC. Cependant, les résultats des essais thérapeutiques rapportés à date ont montré une myélosuppression significative chez certains patients. *Méthodes:* 19 patients atteints de SEPPC sévère (score moyen à l'échelle d'invalidité EDSS = 6.7) ont été traités sur une base humanitaire avec la cladribine à la dose de 0.07 mg/kg/jour par voie s.c. pendant 5 jours par cycle, à toutes les 4 semaines, pour un total de 6 cycles. Les patients ont subi une évaluation clinique, EDSS, et des analyses hématologiques avant, pendant et après le traitement. *Résultats:* Le traitement a été très bien toléré, sans effet secondaire cliniquement significatif. Entre la phase pré-traitement et la fin du sixième cycle, des diminutions moyennes du décompte absolu des lymphocytes de 1697 à 463 ($p = 0.000012$), du décompte CD4 de 865 à 187 ($p = 0.0000008$), du décompte CD8 de 418 à 165 ($p = 0.005$) et CD19 de 197 à 26 ($p = 0.000002$) ont été observées. Le décompte des plaquettes, des granulocytes et des globules rouges n'était pas atteint. Environ un an après la fin du traitement, une récupération du décompte CD4 et CD8 était évidente, bien que ces deux décomptes demeuraient supprimés en comparaison avec ceux de la phase pré-traitement (302 et 227 respectivement); le décompte CD19 était revenu à la normale à un an. Les scores EDSS post-traitement ont montré une détérioration chez 8 patients et des scores stables chez les 11 autres. L'évaluation globale du traitement par les patients était mixte. *Conclusions:* La cladribine s.c., à dose plus faible que dans les études rapportées antérieurement, a été remarquablement bien tolérée chez les patients atteints de SEPPC, sans myélosuppression significative. Des effets marqués ont été notés sur le décompte lymphocytaire total et sur les sous-populations CD4, CD8 et CD19.

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BACKGROUND

There is considerable evidence that cell mediated immunity plays an important role in the pathogenesis of multiple sclerosis (MS). Helper (CD4) T lymphocytes are found in MS lesions

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along with abnormal MHC class II expression.^{1,2} In experimental allergic encephalomyelitis (EAE), injection of myelin basic protein (MBP) and other myelin proteins results in T-cell infiltration into the CNS, accompanied by CNS lesions similar to those seen in MS.³ T lymphocytes specific to such myelin antigens have been shown to induce CNS inflammation in several mammalian species.⁴ T lymphocyte clones reactive to MBP have also been found in the blood of patients with MS.⁵ Despite these observations the exact mechanisms of demyelination are unclear.

Beta interferons have been shown to reduce the frequency and severity of exacerbations in the relapsing remitting form of MS.⁶ However, little progress has been made in altering the natural history of the disease particularly in patients with chronic progressive MS. Despite early encouraging results, immunosuppressive agents such as cyclophosphamide, azathioprine, and cyclosporin have demonstrated, at best, only marginal activity in double blind controlled trials.^{7,8,9}

Cladribine (2 - chlorodeoxyadenosine) is a purine analog which is incorporated into DNA and is resistant to the enzyme adenosine deaminase.¹⁰ It has demonstrated considerable anti-neoplastic activity in hairy cell leukemia, chronic lymphocytic leukemia and certain forms of non-Hodgkin's lymphoma.¹¹⁻¹⁴ It has significant immunosuppressive effects, with reduction in the numbers of CD4 and CD8 lymphocytes¹⁰⁻¹³ which persist for 6-12 months or more after a course of therapy. The drug is generally well tolerated with the major toxicity being myelosuppression.^{10,15}

Recently a small (n = 51), randomized, double-blind, placebo controlled, cross-over trial was reported using intravenous cladribine in patients with CPMS.¹⁶ 48 patients entered as matched pairs and the trial was stopped after one year of treatment before the cross-over occurred. Treatment consisted of four monthly cycles of 0.7 mg/kg cladribine given through a central line. Cladribine appeared to favourably influence the course of CPMS, with improvement or stabilization in neurological scores, lesion volumes on MRI, and concentrations of oligoclonal bands in cerebrospinal fluid in treated patients, compared to placebo. However, although the treatment was generally well tolerated, significant hematologic toxicity was reported, in addition to several viral infections.¹⁵

Subcutaneous cladribine has shown good bioavailability compared to the intravenous route, with a similar pharmacokinetic profile.¹⁴ Our objective was to evaluate the safety and tolerability of subcutaneous cladribine therapy in patients with chronic progressive multiple sclerosis, and to assess if lower doses than those previously used would be immunosuppressive with less myelosuppression.

PATIENTS AND METHODS

19 patients (13 females and 6 males) with chronic progressive MS (CPMS) attending the MS Clinic at St. Michael's Hospital in Toronto were treated. EDSS scores ranged from 5.5 to 8, and ages from 31 to 60 years (mean age 43). Patients were selected for treatment on compassionate grounds based primarily on rapid progression in the two years prior to therapy.

The average disease duration in these patients was 12.6 years. 15 patients had no comorbid medical conditions. The following conditions were found in one patient each: asthma, insulin-dependent diabetes mellitus (IDDM), depression, and

IDDM with depression. Most patients had at some point in their disease been treated with short term high dose corticosteroids for MS exacerbations. Apart from brief courses of corticosteroids, no patient had received immunosuppressive therapy in the year prior to the study. No patient received concomitant corticosteroid or other immunosuppressive therapy while on cladribine. Cladribine (Leustatin7®, Ortho-Biotech) was administered at a dose of 0.07 mg/kg/day by subcutaneous injection for 5 days per cycle, or 0.35 mg/kg/cycle, repeated every 4 weeks for 6 cycles in total. Complete blood count (CBC) and differential, as well as clinical assessment, were done prior to each treatment cycle; CBC was repeated at day 14 following at least the first cycle to assess the nadir counts. Total lymphocyte counts and CD4, CD8 and CD19 positive lymphocyte subsets were determined prior to initiation of treatment, then at Cycle 3 and 6, and (in most instances) at one year following completion of therapy. Lymphocyte subset analysis was done by immunophenotyping using a FACScan flow cytometer. The normal reference ranges for total lymphocyte count, CD4, CD8 and CD19 subsets were 1500 – 2900, 535 – 1125, 300 – 810 and 135 – 447 x 10⁶/L respectively.

Neurologic assessments and EDSS scores were performed by neurologists at the MS clinic at baseline, during therapy, after completion of the 6 cycles, and in follow-up over the next 21 months. Because of difficulties involved in getting significantly disabled patients to return for follow-up, the exact timing of the EDSS assessment varied somewhat.

Data are presented as mean "± standard deviation. The Student's t-test for paired data was used to compare observations; a significance level of 0.05 was used to indicate statistical significance.

RESULTS

Of the 19 treated patients, 13 received all six cycles of cladribine. Six patients chose not to complete therapy, 2 patients after 5 cycles, 3 after 4 cycles and 1 after 3 cycles. The primary reasons patients gave for not completing therapy were perceived lack of efficacy together with the medication cost. Toxicity did not limit treatment in any of the cases.

Laboratory data from 4 patients (patients 2, 8, 10 and 13 on Table 3) were excluded from analysis because of absent baseline lymphocyte subset data in two cases, and insufficient follow-up data in the other two. The total lymphocyte count and CD4, CD8 and CD19 lymphocyte subsets at baseline (prior to the start

Table 1: Lymphocyte subset analysis during therapy (n = 15).

	Baseline	3 Months	p value*	6 months	p value**
Lymphocyte count	1697 ± 570†	801 ± 350	0.0000007	463 ± 207	0.000012
CD4 count	865 ± 313	411 ± 170	0.000005	187 ± 94	0.0000008
CD8 count	418 ± 170	248 ± 145	0.00002	165 ± 127	0.005
CD19 count	197 ± 104	25 ± 27	0.000002	26 ± 16	0.4

P value derived from Student's t test for paired data

*Baseline vs. 3 months

**3 months vs. 6 months

†All values expressed as mean ± standard deviation, x 10⁶/L.

of cladribine therapy), and at 3 and 6 months on therapy in the 15 evaluable patients are summarized in Table 1. As shown, significant decreases in total lymphocyte counts as well as in helper (CD4+) and cytotoxic/suppressor (CD8+) lymphocyte subsets were seen during cladribine therapy. There was a continuing decline in T lymphocyte subsets from 3 to 6 months; this was particularly true for the CD4 subset. Highly significant decreases in the B lymphocyte (CD19+) subset was also seen with trough values attained at 3 months.

Follow up laboratory data, one year after completion of cladribine, were available on 12 of these 15 patients and are summarized in Table 2. The mean total lymphocyte, CD4 and CD 8 counts had shown some recovery compared to the values at the end of therapy, but were still significantly below baseline level. The mean CD19 count had recovered to normal levels.

Table 2: Lymphocyte subset analysis following completion of therapy (n=12).

	6 Months	1 year post therapy	p value*
Total Lymphocyte count	475 ± 200†	895 ± 367	0.0003
CD4 count	199 ± 97	302 ± 133	0.018
CD8 count	156 ± 91	227 ± 142	0.047
CD19 count	28 ± 16	179 ± 110	0.00014

*P value derived from Student's t test for paired data

†All values expressed as mean ± standard deviation, x 10⁶/L.

Table 3: Summary of EDSS scores obtained on cladribine therapy; 0 months represents baseline (n = 19).

Pt. #	cycles	Months from start of therapy									
		0	3	6	9	12	15	18	21	24	27
1.	6	7.5						8.5			
2.	6	7							7		
3.	6	6			6	6					
4.	6	8	8				8.5		8.5		
5.	6	8					8.5				
6.	6	6.5	6.5	6.5	6.5	6.5					
7.	6	6.5	6.5	7			7	6.5			
8.	6	6.5							6.5	7	
9.	6	6			6	6					6.5
10.	6	6.5			6.5	6.5					
11.	6	6		6			6.5	6			
12.	6	6.5		6.5				7			
13.	4	7		7			7		7.5		
14.	6	7		7			7		7		
15.	5	7			7	7	7				
16.	5	7					7				
17.	4	7.5	8.5					8.5			
18.	4	6.5	6.5					7			
19.	3	5.5	5.5	5.5							

There were no opportunistic infections seen either during cladribine therapy or in the following year. The hemoglobin, granulocyte and platelet counts were within normal reference ranges throughout the duration of cladribine therapy. One female patient developed a borderline anemia with a hemoglobin of 117 g/L while on cladribine which recovered to normal post therapy. Another patient had a mild thrombocytopenia with a platelet count of 136 x10⁹/L, after one cycle of cladribine which returned to normal by the subsequent 2 cycles.

No definite nonhematologic toxicity was reported or observed. No patient required a reduction of cladribine dose or treatment delay secondary to adverse effects.

Details of EDSS scores are in Table 3. A significant change in EDSS score was defined as a change of one-half point or more measured at the first post therapy visit and compared to baseline. Follow-up data are available in all patients, at times varying from 6-21 months after completion of therapy. Of these, 8 patients had an EDSS score that increased significantly as compared to baseline, while 11 were unchanged. None had a significantly lower EDSS. Patient global rating scores obtained approximately 1 year after therapy indicated that 5 patients felt they were doing better, 3 were unchanged and 9 worse; the remaining 2 were uncertain.

DISCUSSION

Cladribine is recognized to have significant immunosuppressive effects, characterized by marked reductions in T and B lymphocyte subsets, when used in the treatment of hematologic malignancies. Myelosuppression is the major toxicity. In the original report of cladribine treatment in MS, a statistically significant drop in blood counts was observed.¹⁵ In 7 patients, the platelet count dropped below 80 x10⁹/L, while a substantial and sustained decrease in granulocytes was seen.¹⁵ Two patients developed severe and prolonged aplastic anemia requiring red cell and platelet transfusions. In one case, the patient had received prior therapy with carbamazepine and was receiving phenytoin while on cladribine. The second patient had previously received extensive therapy with chlorambucil. Both recovered after several months of marrow suppression. Two patients developed herpes zoster which subsided rapidly on acyclovir treatment. One patient presented with acute fulminant hepatitis B infection 3 days after her second cladribine infusion and died 5 days after admission. She had negative hepatitis B serology at start of therapy and a history of probable recent exposure.

Our series of patients received a lower total treatment dose (total of 2.1 vs 2.8 mg/kg, as well as a lower treatment dose per cycle (0.35 mg/kg vs. 0.7 mg/kg). Using this dosing regimen, patients experienced no significant myelosuppression or infectious problems despite achieving profound lymphocyte suppression. When compared to the higher dose regimen, the rate of decline in the CD4 count using our regimen was less rapid, although the trough CD4 count at six months into treatment was similar.¹⁵ In contrast, the rate of decline, nadir and post-therapy levels of CD8 and CD19 counts were similar in the two groups. At approximately 1 year post-therapy, we noted a partial but incomplete recovery in CD4 counts, while CD4 levels remained severely depressed in the higher-dose study.¹⁵ In view of the presumed pathogenetic role of T helper cells in MS,^{1,2} the slower decline and earlier recovery in these cells could have implications

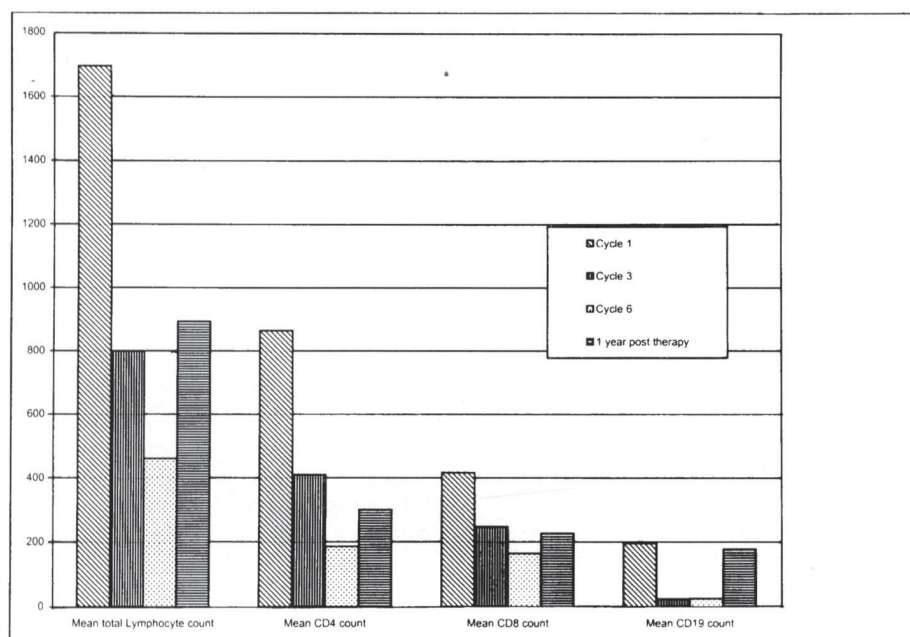


Figure 1: Absolute lymphocyte count and lymphocyte subsets - CD4, CD8 and CD19 at baseline, 3 months and 6 months while on Cladribine therapy, and 1 year after completion of Cladribine.

regarding therapeutic efficacy. However, since only a small subset of T cells is likely involved in producing MS, these implications are unclear. Measuring T lymphocytes reactive to myelin basic protein⁵ could address this question *in vitro*, although only a randomized trial could accurately assess the clinical relevance of the effects of the different dosing regimens.

In addition to the lower cladribine dose, none of our patients were on concomitant immunosuppressive or myelosuppressive therapy which may have contributed to the lack of toxicity. Concomitant use of corticosteroids and purine analogs has been associated with opportunistic infections.¹⁷ Whether cladribine is safe to use along with or soon after medications such as beta-interferon, methotrexate, azathioprine or cyclophosphamide is unclear and requires further study. The long-term safety of cladribine in MS is also unknown.

The subcutaneous route of administration has been shown to have a favorable pharmacokinetic profile, with 100% bioavailability and no local toxicity.¹⁴ Such treatment is easy to administer, not requiring intravenous access. Although given in our Medical Day Care outpatient unit, there is no reason in principle why patients could not be trained in self-administration of the medication.

Subcutaneous cladribine therapy, at the doses used in this study, is remarkably well tolerated in chronic progressive multiple sclerosis, with no significant toxicity despite achieving profound and long lasting immunosuppression. The degree of suppression of lymphocytes was similar to the higher-dose regimens, although differences were noted in the rate of decline and recovery of CD4 counts.

As this was a safety and tolerability study with no control group, nothing meaningful can be stated regarding the observed EDSS changes, given the unpredictable course of MS. Although no objective improvements were noted in any patient, we cannot exclude the possibility that cladribine may have contributed to

disease stabilization in some instances. We await the results of a large appropriately powered randomized blinded trial of this medication with interest. Although safe and easy to use, the therapeutic effectiveness of cladribine in chronic progressive MS remains to be established.

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