

Cladribine

Use in Therapy of Multiple Sclerosis

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Summary

Cladribine is a novel drug that selectively depletes lymphocytes and may be able to destroy the activated immunocytes that damage the central nervous system in multiple sclerosis. Our initial controlled studies have shown a beneficial, although temporary, dose-related effect of cladribine on the course of chronic progressive multiple sclerosis.

Peak improvement in median Scripps Neurological Rating Scale (SNRS) neurological performance scores, followed by gradual decline, occurred at month 14 after initiation of treatment with a 2.8 mg/kg total dose and at month 7 after initiation of treatment with a 1.4 mg/kg total dose. A marked decrease in the presence of enhanced magnetic resonance imaging lesions was observed at both dose levels.

Adverse effects are also dose-related. Mild segmental herpes zoster or transient marrow suppression occurred in some patients treated at the higher total dose, whereas no problems of this kind were observed at the lower total dose.

It is our hope that studies that are presently under way will establish cladribine as a practical therapeutic option for patients with all non-benign forms of multiple sclerosis.

The fundamental cause of multiple sclerosis is still unknown, but there is persuasive circumstantial evidence that immunopathological mechanisms play an important role in the inflammatory demyelination of the central nervous system (CNS) which is the hallmark of the disease.^[1] Suppression and/or 'modulation' of the immune system is there-

fore a rational means of therapy for multiple sclerosis.^[2]

Although interferon- β has recently been shown to decrease the frequency and severity of relapses in the relapsing-remitting form of multiple sclerosis,^[3] no clearly satisfactory treatment by immunosuppression or any other method has yet been

Table I. Completed and ongoing clinical trials of cladribine in the treatment of multiple sclerosis

Trial	Type of multiple sclerosis	Blinded/crossover	Dosage and duration (daily dose × number of days)	Route	Number of courses	Trial location	Comments and references
1 ^a	CP	No/no	0.087 mg/kg × 7	IV	6	Scripps	Feasibility study in 4 patients in 1990
2 ^a	CP	Yes/yes	0.1 mg/kg × 7	IV	4	Scripps	Part I of double-blind crossover study ^[12]
			0.1 mg/kg × 7 0.05 mg/kg × 7	IV IV	1 2	Scripps	Part II of double-blind crossover study ^[13]
3 ^b	RR	Yes/no	0.07 mg/kg × 5	SC	6	Scripps	
4 ^b	CP	Yes/no	0.07 mg/kg × 5	SC	2 and 6	Multicentre in US and Canada	
5 ^b	CP	Yes/no	0.05 mg/kg × 5	SC	4	Scripps	Retreatment study of patients from trial 2 ^[21]
6 ^b	RR	Yes/no	5mg × 5 10mg × 5	SC Oral	6	Polish Academy of Science	

a Completed study.

b Ongoing study.

Abbreviations: CP = chronic progressive; IV = intravenous; RR = relapsing remitting; SC = subcutaneous.

found for patients with chronic progressive multiple sclerosis (CPMS). Previous trials of treatment in CPMS have involved broad-spectrum immunosuppressive drugs such as cyclophosphamide^[4] and methotrexate.^[5] The modest benefit observed with these drugs has been generally counterbalanced by concerns over toxicity.

One current hypothesis of multiple sclerosis pathogenesis is that activated T lymphocytes pass from the bloodstream into the multiple sclerosis plaques in the CNS. These activated cells, regardless of their immune specificity, may directly or indirectly damage myelin and/or oligodendrocytes. Therefore, the selective depletion of lymphocytes in multiple sclerosis might be beneficial if it could be accomplished safely. For these reasons, a new type of drug, cladribine (2-chlorodeoxyadenosine, Leustatin[®]), was selected for trial in CPMS because of its properties of relatively selective production of lymphopenia with a favourable toxicity profile as compared with other antilymphocyte drugs.^[6]

Cladribine is an adenosine deaminase-resistant purine nucleoside that was developed by Carson et al.^[7] at Scripps Clinic and Research Foundation. The drug was designed to simulate the immunodeficient condition seen in the rare disorder of he-

reditary adenosine deaminase deficiency by causing high levels of deoxynucleotides to accumulate in lymphocytes, thus resulting in cell death. In contrast with other antilymphocyte agents, cladribine has the ability to kill both resting and dividing cells.^[8]

The use of cladribine in CPMS was considered following pioneering clinical studies with cladribine at the Scripps Clinic in the treatment of various lymphoid neoplasms and leukaemia.^[9] The most dramatic positive results were seen in hairy cell leukaemia, in which 86% of patients experienced a durable and complete remission after a single treatment with cladribine.^[6] Cladribine is also presently under evaluation at our institution in a variety of autoimmune disorders, including Coomb's positive haemolytic anaemia, immune thrombocytopenia, rheumatoid arthritis and inflammatory bowel disease.

The bioavailability of cladribine is the same by either continuous intravenous or intermittent subcutaneous administration, and is halved when given by the oral route.^[10] A detailed discussion of the clinical pharmacokinetics of cladribine has been presented elsewhere.^[11]

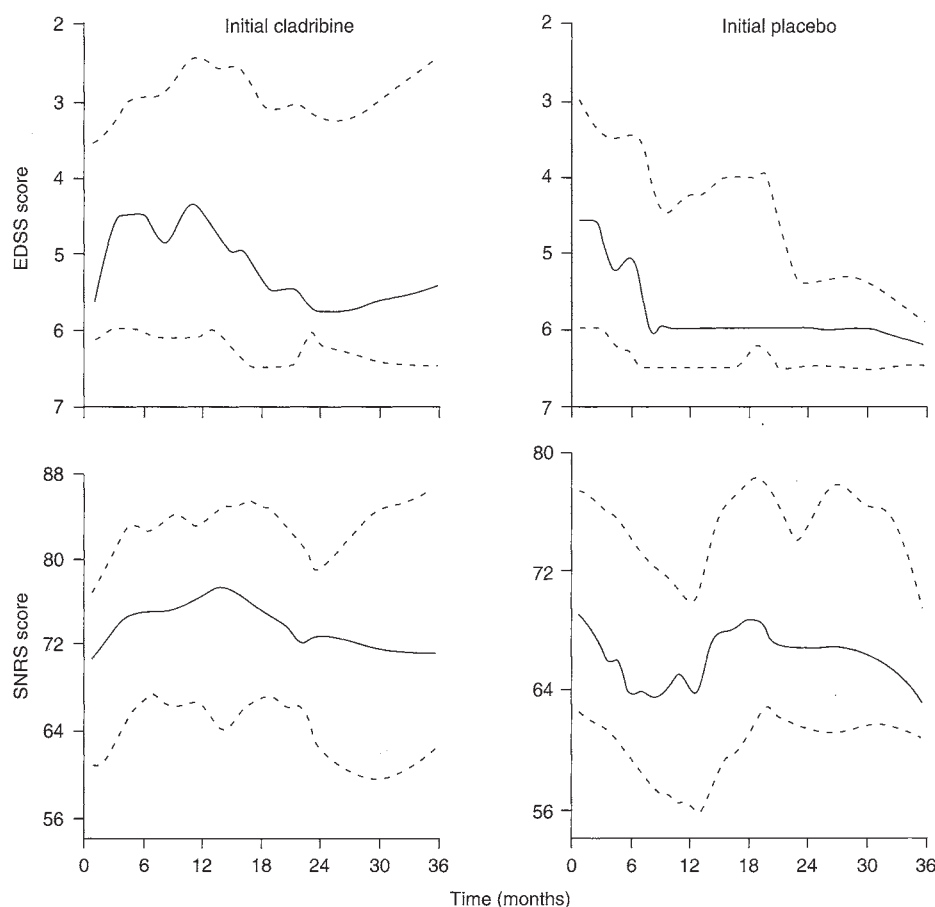


Fig. 1. Kurtzke Extended Disability Status Scale (EDSS) [top] and Scripps Neurological Rating Scale (SNRS) [bottom] scores of 48 patients with chronic progressive multiple sclerosis treated with cladribine in a double-blind crossover study. The initial cladribine group (left) received cladribine 0.7 mg/kg as a continuous intravenous infusion over 7 days in each of 4 successive months. The initial placebo group (right) was given cladribine 0.7 mg/kg as the first monthly infusion in month 13, and 2 subsequent 7-day infusions of 0.35 mg/kg in months 14 and 15. Medians (solid lines) and interquartile ranges (broken lines), smoothed with the nonparametric procedure LOWESS, are shown.

1. Results in Chronic Progressive Multiple Sclerosis

An initial feasibility study with 4 patients in 1990 was encouraging, and we subsequently conducted a double-blind crossover study of the effect of cladribine in CPMS (table I). To date, this is the only controlled study of cladribine in multiple sclerosis to be completed; the results have been published in 2 parts.^[12,13]

In this study, 48 patients with CPMS were paired by age, gender and disease severity. Pair

members were randomly assigned to receive either cladribine or placebo treatment via surgically implanted venous access devices. Patients on the cladribine arm were given monthly 7-day continuous intravenous infusions of cladribine 0.1 mg/kg/day (0.7 mg/kg/course) for a total of 4 courses (total dose 2.8 mg/kg). Patients on the placebo arm were given saline intravenously in an identical fashion. Double-blind masking was maintained; patients, neurologists, neuroradiologists and nurses had no knowledge of which medication

a patient was receiving. Patients were examined monthly and 2 neurological performance scores were recorded [Kurtzke Extended Disability Status Scale (EDSS)^[14] and Scripps Neurological Rating Scale (SNRS)^[15]].

Over 12 months, analysis of SNRS and EDSS scores showed progressive deterioration during the first year in patients receiving placebo, while the median SNRS and EDSS scores of patients receiving cladribine improved modestly. Absolute changes in neurological scores were favourable in both EDSS ($p = 0.013$ at 12 months) and SNRS ($p = 0.001$ at 12 months) scoring systems (fig. 1). Statistical significance in favour of cladribine was also established when 12 months of data were analysed by Kaplan-Meier time-to-failure plots (fig. 2).^[13]

Blinding was maintained and the study was continued for a second year of treatment and observation. However, patients were crossed over to oppo-

site treatment arms. Patients treated with cladribine in the first year received placebo in the second year, and vice versa. However, the dosage of cladribine was reduced to one-half of that given during the first year. The reduced total dose of cladribine 1.4 mg/kg was administered by continuous intravenous infusion in divided doses as follows: 0.7 mg/kg for the first monthly course, 0.35 mg/kg for the second and third courses, and saline placebo for the fourth course. Patients who had received cladribine in the first year were given 4 monthly infusions of saline placebo.

Results from the second year are also illustrated in figure 1. Comparison of data from years 1 and 2 of the study reveals that patients who had first received placebo and then crossed over to treatment with the lower dose of cladribine (1.4 mg/kg) show a trend of improvement in SNRS scores similar to that seen in patients treated with the full (2.8 mg/kg) dose. Similar comparison also suggests

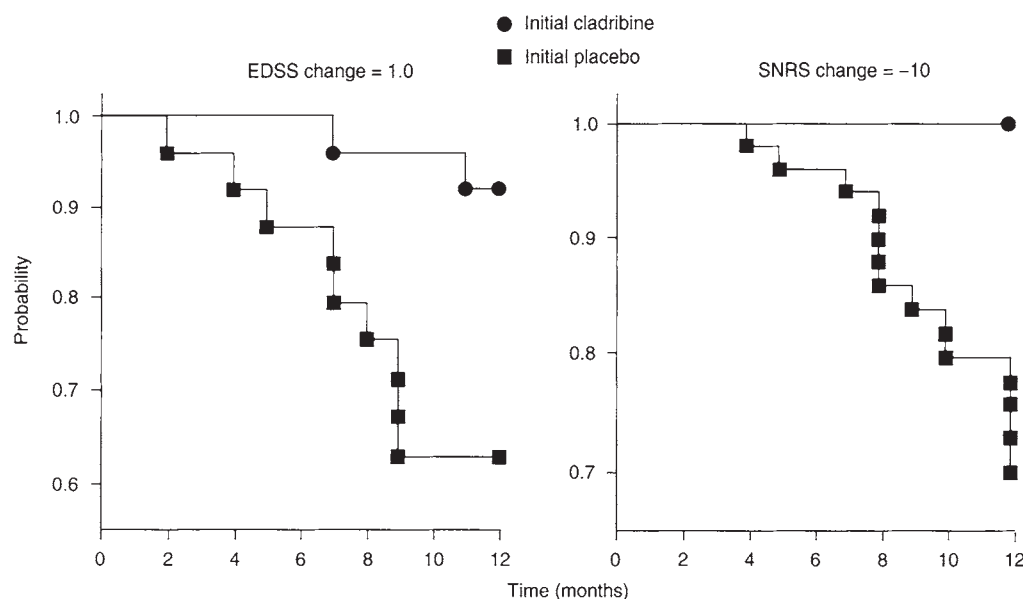


Fig. 2. Kaplan-Meier time-to-failure plots of patients with chronic progressive multiple sclerosis treated with cladribine in a double-blind crossover study. (**Left**) Time to failure as defined by an increase of Kurtzke Extended Disability Status Scale (EDSS) score by 1.0 point on at least 2 consecutive months, considering the first month of change as the time of event. (**Right**) Time to failure as defined by a decrease of Scripps Neurological Rating Scale (SNRS) score by 10 points on at least 2 consecutive months, considering the first month of change as the time of event. The difference in time to failure estimated by log-rank statistics was significant for both scoring systems in favour of cladribine (EDSS, $p = 0.0148$; SNRS, $p = 0.001$).

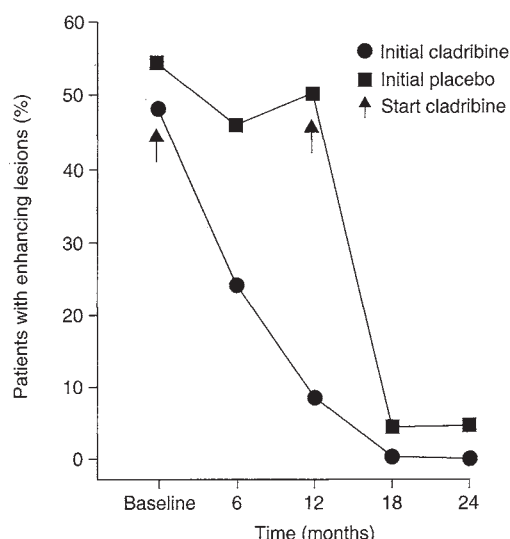


Fig. 3. Proportion of patients with enhancing lesions over the course of a double-blind crossover study of cladribine treatment of chronic progressive multiple sclerosis. The difference was significant in favour of cladribine at 12 and 24 months ($p < 0.001$ by McNemar's test).

that stabilisation of disease may be of shorter duration with the lower dose of cladribine. Peak improvement of median SNRS scores, followed by gradual decline, occurred at month 14 after initiation of treatment with the 2.8 mg/kg total dose and at month 7 after initiation of treatment with the 1.4 mg/kg total dose. Statistical analysis of the variance of paired differences in EDSS and SNRS scores from year 2 of the study again confirmed significant treatment effects in favour of cladribine.^[16]

Magnetic resonance imaging brain scans were obtained after intravenous gadopentetate dimeglumine at baseline and at 6, 12, 18 and 24 months. Volumetric analysis of demyelinated (T_2 -weighted) lesions revealed no significant differences between the cladribine and placebo groups. However, a highly significant difference in favour of cladribine was documented when the number of 'active' lesions (lesions enhanced by gadopentetate) were analysed (fig. 3). Approximately one-half of the patients in both the initial cladribine-treated and the initial placebo-treated groups had enhanc-

ing lesions at baseline. At 18 and 24 months after initiation of treatment with cladribine 2.8 mg/kg total dose, no patient had lesion enhancement. In patients treated initially with placebo, lesion enhancement persisted at the same percentage level at months 6 and 12, but after treatment with cladribine 1.4 mg/kg total dose, lesion enhancement was subsequently observed in only a single patient.

2. Adverse Effects

As of June 1995, a total of 125 multiple sclerosis patients (both chronic progressive and relapsing/remitting multiple sclerosis) have been treated at Scripps Clinic. The adverse events observed to that date in association with cladribine treatment are summarised in table II. Most patients had no obvious drug-related symptoms or signs in association with the administration of cladribine. However, 8 patients, all treated with the full 2.8 mg/kg dose, developed mild segmental herpes zoster. No other opportunistic infections occurred. 3 patients treated with the 2.8 mg/kg dose developed transient bone marrow suppression with low platelet counts; 2 of these patients required hospitalisation for red cell and platelet transfusion. One patient died of acute fulminant hepatitis B during the second month on cladribine, an event previously reported and considered to be probably unrelated to treatment.^[12]

The details of the effect of cladribine on blood counts in these patients are reported elsewhere.^[17] As expected, profound and prolonged lymphocyte depletion (most notably CD4+ cells) occurred in cladribine-treated patients; other blood cellular components were less affected. Granulocyte counts showed only a minor decline and the average haemoglobin level declined moderately, with significant anaemia due to transient bone marrow suppression in only a single patient. However, red cells generally became macrocytic, especially at the higher dose levels. Average platelet counts declined to a low of around $1.5 \times 10^9/L$, with recovery to near normal levels by 12 months after treatment. Monocyte counts dropped within days of drug ad-

Table II. Adverse events in 125 multiple sclerosis patients treated with cladribine^a

Adverse event	Age (y)/gender	Treated as part of study protocol?	Cause	Total dose of cladribine (mg/kg)	Event due to cladribine treatment?
Death					
	40/F	Yes	Acute hepatic necrosis secondary to hepatitis B	1.4	Unlikely
	43/F	Yes	Suicide	2.8	No
	31/F	Yes	Drowning in pool	2.8	No
	47/M	No	Quadriplegia and respiratory failure secondary to progressive multiple sclerosis	2.1	No
Marrow suppression					
	43/F	Yes	Cladribine ^b	2.8	Yes
	67/F	No	Cladribine ^c	2.1	Yes
Infections					
	41/F	Yes	Streptococcal pharyngitis	2.8	No
	43/F	Yes	Herpes zoster	2.8	Yes
	57/F	Yes	Herpes zoster	2.8	Yes
	39/M	Yes	Herpes zoster	2.8	Yes
	46/F	Yes	Herpes zoster	2.8	Yes
	51/F	Yes	Herpes zoster	2.8	Yes
	47/M	No	Herpes zoster	2.8	Yes
	50/F	Yes	Herpes zoster	2.8	Yes
	52/F	Yes	Herpes zoster	2.8	Yes
Thrombocytopenia					
	4 patients	Yes	Cladribine	2.8	Yes
Revision of Portacath					
	58/F	Yes	Portacath malfunction	2.8	No
	43/F	Yes	Portacath malfunction	2.8	No
	40/F	Yes	Portacath malfunction	2.8	No
	40/F	Yes	Pneumothorax	2.8	No

a Patients treated from 1990 to June 1995.

b Previous treatment with carbamazepine and phenytoin.

c Previous treatment with chlorambucil.

Abbreviations: F = female; M = male; y = years.

ministration, with rebound to near normal levels within 1 month.

In summary, the adverse effects seen in this group of multiple sclerosis patients are dose-related. All episodes of mild herpes zoster and occasional episodes of transient marrow suppression occurred in association with the 2.8 mg/kg dose, while none occurred in patients treated with the 1.4 mg/kg dose. Two of the patients with temporary marrow suppression had been previously treated with potentially marrow-suppressive drugs, one with carbamazepine and phenytoin, the other with chlorambucil. This would suggest that the risk of

marrow suppression from cladribine is increased after previous treatment with drugs, such as those above, which can reduce the size of the haemopoietic stem cell pool.

Previous studies of cladribine treatment of patients with neoplastic disorders have shown that increasing doses of cladribine are associated with an increased incidence of thrombocytopenia as well as marrow suppression with pancytopenia. At total doses 5 to 10 times that used for hairy cell leukaemia (as part of preparation for bone marrow transplantation), renal dysfunction and CNS toxicity were observed, the latter manifested as

paraparesis or quadraparesis usually occurring several weeks after cladribine treatment.^[6,18,19] No such neurological or renal toxicity has been seen in any of the thousands of patients with lymphoid malignancies treated with cladribine at lower doses comparable with those used in our multiple sclerosis studies.

There are other possible adverse effects which have not yet been seen with cladribine but which are of concern. The possibility over the long term for induction of a neoplastic disorder after treatment with cladribine is a consideration, since the drug is incorporated into DNA. At the present time there has been no obvious increase in the frequency of secondary neoplasms occurring in over 5000 cancer patients treated worldwide with cladribine, although the possibility of such a phenomenon has not been excluded since no formal study has been performed. Likewise, the use of cladribine together with other immunosuppressive drugs, including high-dosage corticosteroids, should be approached with caution since the additive immunosuppressive effect of such a combination could lead to a higher incidence of herpes zoster or other opportunistic infections. Although this problem has not been observed with cladribine, it should be considered a possibility in view of the reported occurrence of an increased incidence of *Listeria* infection in cancer patients treated with fludarabine, a purine nucleoside drug related to cladribine, plus prednisone.^[20]

3. Therapeutic Potential and Clinical Use

The evaluation of cladribine as a treatment for multiple sclerosis is still in progress. At this time it is not licensed for the treatment of multiple sclerosis and remains an experimental therapy best limited to clinical trials. Whether or not it proves to be a practical treatment for multiple sclerosis will depend on the results of several ongoing studies which are presently under way at sites including Scripps, a multicentre trial in the US and Canada, and the Polish Academy of Science^[21] (table I). These studies include further controlled trials with CPMS patients as well as patients with the relaps-

Table III. Pretreatment safety criteria for monthly courses of cladribine in multiple sclerosis

Platelet count must be:
$\geq 2.0 \times 10^{11}/L$ or
1.5 to $2.0 \times 10^{11}/L$ and $>50\%$ of previous pretreatment platelet count or
1.25 to $1.5 \times 10^{11}/L$ and $\geq 80\%$ of previous pretreatment platelet count
Absolute granulocyte count must be $>10^9/L$
Haemoglobin level must not have declined by:
>15 g/L from previous monthly pretreatment level or
>30 g/L from baseline

ing/remitting form of multiple sclerosis. Since the beneficial effect of a single course of cladribine in CPMS patients is not permanent, a current study of the safety and efficacy of retreatment with cladribine will be especially important.

At our institution, current trials with cladribine in multiple sclerosis are now proceeding with the subcutaneous route of administration rather than the more invasive continuous intravenous method used in earlier studies. Subcutaneous cladribine is well tolerated and produces no local reaction at injection sites. Because cladribine solutions are currently available only at a concentration of 1 mg/ml, the total volume for each daily dose is normally divided into 2 or 3 subcutaneous injection sites in the abdomen or thigh to prevent administration of too large a volume at 1 site. A preparation more suitable for clinical use, which contains 5mg of cladribine per ml, is now in clinical trial.

We do not enter into a study any multiple sclerosis patient who has abnormal baseline haematological, hepatic or renal functions. Individual monthly treatments of cladribine are given only if certain pretreatment blood count safety criteria are met, as outlined in table III. If treatment safety criteria are not met, then the treatment is withheld for that monthly cycle and given the following month if blood count criteria are met at that time. Complete blood counts are also checked periodically in the 8 weeks after completion of the cladribine treatment cycle.

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