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Cladribine

A Review of its Use in Multiple Sclerosis

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Summary

Cladribine is a deaminase-resistant deoxyadenosine analogue that selectively reduces lymphocyte counts. The drug is an effective therapy for selected haematological malignancies and is being tested in patients with multiple sclerosis (MS),

in whom the antilymphocytic effects of the drug may reduce the autoimmune destruction of myelin.

With activity against resting and dividing cells that express high deoxycytidine kinase activity, cladribine causes prolonged, profound suppression of lymphocyte counts. Subcutaneous cladribine is 100% bioavailable and has no local tissue toxicity. Dosages used in clinical trials in patients with MS are in the range of 0.05 to 0.07 mg/kg/day subcutaneously for 5 days each month for 2 to 6 months.

Temporary improvement or no change in neurological functioning and improvements in CNS lesions detected by gadolinium-enhanced magnetic resonance imaging (MRI) have been seen after cladribine use in patients with chronic progressive (CPMS) and relapsing-remitting (RRMS) forms of MS. In a randomised double-blind study of 24 pairs of patients, improvement or stabilisation of CPMS for ≈2 years was observed in cladribine-treated patients, whereas the disease progressed in placebo recipients. Another study of 159 patients found no progression in either the treated or placebo control group. In both studies, marked improvements were seen in gadolinium-enhanced CNS lesions. Cladribine-associated improvements in neurological functioning were also seen in some patients with RRMS in one study, which also noted a reduction in the frequency and severity of relapses. In this and a separate RRMS study, cladribine resulted in the regression of CNS lesions on MRI.

Bone marrow suppression is the main dose-related toxicity; in patients with MS, use of low total cladribine dosages appears to limit myelosuppression. Although thrombocytopenia is of concern with higher-dose regimens (i.e. 2.8 mg/kg total dose) in patients with MS, granulocyte counts and haemoglobin levels appear to be largely unaltered. Cladribine treatment is also associated with culture-negative fever and a risk of infections in patients with haematological malignancies.

Conclusions: Further study of cladribine is needed to confirm present results in wider numbers of patients treated or followed up for longer durations, define optimum treatment and retreatment schedules for the drug and compare it with other agents. Nonetheless, cladribine therapy appears to have the potential to slow the progression of MS, reduce CNS lesions in patients with either the chronic progressive or relapsing-remitting forms of the disease and improve neurological functioning in some of these patients.

1. Rationale for the Use of Cladribine in Multiple Sclerosis

Multiple sclerosis (MS) is characterised by clinical signs and symptoms of CNS demyelination including optic neuritis, diplopia, muscle weakness, spasticity and eventual loss of ambulatory function. The disease may have relapsing and remitting stages (RRMS) or can be chronic and progressive (CPMS).[1,2] However, progressive disease may occur without a relapsing-remitting stage (primary progressive) or may follow a relapsing-remitting stage (secondary progressive).[3] The disease is highly variable in its course, and although it causes considerable disability, it does not greatly reduce life expectancy, except in patients with severe disability.[4]

A diagnosis of MS must be based on symptoms characteristic of at least 2 CNS lesions. Tests that assist in diagnosis and evaluation of the progression of MS include examination of the CSF for the presence of oligoclonal bands of IgG and magnetic resonance imaging (MRI) for CNS lesions.[5] Neurological impairment is often assessed using the Kurtzke extended disability status scale (EDSS), although the Scripps neurological rating scale

(SNRS) and other similar tests have also been used.[2] For a more detailed description of the functions of these tests, see section 3 and the review by Waubant and Goodkin.[2]

Cladribine (2-chloro-2′-deoxyadenosine) is an adenosine deaminase–resistant analogue of deoxyadenosine. After phosphorylation to cladribine triphosphate within cells by the enzyme deoxycytidine kinase (dCK), it is incorporated into DNA, where it takes the place of adenosine triphosphate and effectively halts cell replication.[6] Phosphorylated cladribine can be dephosphorylated (and therefore inactivated) by 5′-nucleotidase (5-NT). Of various cells of the body, lymphocytes are most subject to the effects of cladribine because they have a higher ratio of dCK to 5-NT than other cells. This and other mechanisms confer on cladribine specific antilymphocytic effects that are of clinical utility in the treatment of haematological malignancies (reviewed by Bryson & Sorkin[6]).

Although MS is thought to be a lymphocyte-dependent autoimmune disease, the specific antigens and triggering agents involved in the disease are unknown, so treatments are nonspecific.[7] The rationale for the use of cladribine in MS is that autoantigen-specific T lymphocytes are thought to be activated peripherally before migrating to the CNS, where they mediate damage to myelin.[8] This suggests that a cladribine-induced reduction in the number of lymphocytes may help to slow progression of the disease. The efficacy of cladribine in the treatment of MS has been studied and the evidence relating to its potential use in this disease is reviewed here.

2. Pharmacology

2.1 Pharmacodynamics

2.1.1 Pharmacodynamic Effects and Mechanism of Action

The major pharmacodynamic effects of cladribine are on blood cells and blood progenitor cells, which express high levels of dCK. dCK levels, which correlate with the degree of cladribine phosphorylation, are high in normal leucocytes (120ng dCK/mg protein) and low in other tissues such as stomach mucosa (6 ng/mg).[9] Cladribine also markedly and dose-relatedly inhibits lymphocyte colony-forming and myeloid progenitor cells from normal human peripheral blood and bone marrow *in vitro*.[10] Bone marrow suppression is a dose-limiting adverse effect of cladribine (see section 4).

Cladribine is active against both resting and dividing cells; therefore, at least 2 mechanisms are thought to be involved in its activity.

In dividing cells, cladribine is believed to be incorporated into DNA in its triphosphate form after phosphorylation by dCK. Cladribine appears in much higher concentrations within blood cells than in blood plasma (see section 2.2.1) and its cytotoxic effects on leukaemic cells correlate with the efficiency of its transport across the cell membrane.[11] Within cells, it is phosphorylated by dCK and dephosphorylated by 5-NT; thus, it is not surprising that hairy cell leukaemia (HCL) and chronic lymphocytic leukaemia (CLL) cells from patients with leukaemia who responded to cladribine exhibited higher dCK ($p < 0.01$) and lower 5-NT ($p < 0.05$) levels than those from non-responders.[12] Cladribine is resistant to adenosine deaminase, so phosphorylated forms of the drug accumulate within cells; 80% of a radiolabelled dose was identified as cladribine monophosphate and 10% as the triphosphate in human tonsillar lymphocytes *in vitro*.[13] Incorporation of cladribine triphosphate into the DNA of dividing cells appears to arrest cell division.[6]

In resting cells, cladribine is believed to induce apoptosis, or programmed cell death. DNA fragmentation is known to occur in a dose-related manner when cells from patients with CLL are exposed to cladribine *in vitro*.[14] Cladribine also appears to induce expression of the p53 protein and its downstream target WAF1/CIP1 protein, which have been implicated in the apoptosis response to DNA damage.[15] Apoptosis has also been measured in peripheral blood cells from 3 patients with HCL before and after intravenous cladribine (0.09 mg/kg/day infused for 7 days),[16] rising from 2 to 3.4% at baseline to 20 to 32% after 5 to 14 days.

Table I. Effects of cladribine (CdA) on blood cell counts in patients with multiple sclerosis of the chronic progressive (CPMS) or relapsing-remitting (RRMS) forms

Parameter	Scripps IV CPMS (n = 29; 30mo observation)[19-21]	Scripps SC RRMS (n = ?; 10mo observation)[20]	Polish SC or PO RRMS (n = 11; 18mo observation)[22]	Polish SC RRMS (n = 90; ≈18mo observation)[23]
Dosage	CdA 0.087-0.1 mg/kg/day IV × 7 days q1mo × 4mo	CdA 0.07 mg/kg/day SC × 5 days q1mo × 6mo	CdA 5 mg/day SC or 10 mg/day PO × 5 days q1mo × 6mo, plus 1 or 2 additional courses at 3mo or 6mo intervals in some patients	CdA 5mg od SC × 5 days q1mo × 6mo; then 5mg od × 5 day 3mo later
Lymphocytes	Prolonged profound lymphopenia (especially of CD4+ cells) affecting both T (CD3+) and B (CD19+) cells; decreased CD4+/CD8+ ratio	Prolonged profound lymphopenia	Prolonged and profound decrease (from ≈2.5×10^9 to 1×10^9 cells/L), no correlation between decrease at 6mo and CdA dosage	Decrease to one-third of original counts
Monocytes	Acute transient monocytopenia	?	?	?
Granulocytes	Modest decrease	?	Little mean change (small decrease at 18mo)	'Not reduced significantly'
Haemoglobin	Modest decrease	Modest decrease	No change	?
Cell size	Prolonged macrocytosis	No macrocytosis	Slight macrocytosis in 'some patients', change in average MCV NS except at 18mo	'Some macrocytosis'
Platelets	Sharp decrease in counts for 6mo, nadir at 8mo, counts were $<100 \times 10^9$ cells/L in 7 of 29 patients (24%)	Variable platelet counts, no major change from baseline at 10mo	Decrease, but none $<100 \times 10^9$ cells/L	'Mild' thrombocytopenia 'of no clinical significance'

Abbreviations and symbol: IV = intravenous; MCV = mean corpuscular volume; NS = not statistically significant; od = once daily; PO = oral; q1mo = every month; SC = subcutaneous; ? = not reported.

Additional *in vitro* effects that may contribute to the mechanisms of action of cladribine include modification of the activity of DNA polymerase[17,18] and ribonucleotide reductase[18] and induction of dCK activity.[13] For further discussion of the mechanism of activity of cladribine, see the review by Bryson and Sorkin.[6]

2.1.2 Effects in Patients with Multiple Sclerosis

Cladribine has a clear profile of effects on lymphocytes and other blood cell counts in patients with MS (table I).

A marked and sustained reduction in lymphocyte counts appears to occur regardless of the total cladribine dose, type of MS or route of drug administration. In 4 trials (1 in patients with CPMS and 3 in patients with RRMS),[20-23] subcutaneous, oral or intravenous cladribine use was associated with reductions in lymphocyte counts to ≈1×10^9 cells/L or to at least one-half and up to one-third of baseline counts, and these reductions lasted throughout the 10- to 30-month observation periods.

Effects of cladribine on other haematological parameters (e.g. platelet counts, cell size) appear to be related to the total dose and/or exposure period. They are greatest in patients with CPMS who received total doses of 2.8 mg/kg as 7-day intravenous courses (table I).[20-22] The lesser effects seen in studies of patients with RRMS are not thought to be related to the disease type or the route of administration, but to the lower dosages (0.07 mg/kg or 5mg once daily subcutaneously or 10mg once daily orally) and the shorter courses (5 *vs* 7 days) adopted in the RRMS trials. Indeed, although thrombocytopenia and prolonged macrocytosis occurred with the higher total dose (2.8 mg/kg) in the patients with CPMS, only modest effects on platelet counts and cell size were observed in patients with RRMS receiving lower total doses (2.1

mg/kg) or lower daily dosages for shorter courses (5mg subcutaneously or 10mg orally for 5 days).

Little or no effect was seen on mean granulocyte counts or mean haemoglobin levels in these studies (table I). Monocytopenia was reported in the intravenous study, but was not discussed in reports of the other trials. For a discussion of other adverse effects of cladribine, see section 4.

2.2 Pharmacokinetics

As yet, no pharmacokinetic studies of cladribine have been conducted in patients with MS, but the kinetics of the drug are well studied in patients with haematological malignancies and solid tumours. Most of the pharmacokinetic research has been conducted in Sweden, and the kinetics of cladribine have been reviewed recently by Liliemark.[24] An overview of cladribine pharmacokinetics based on the review of Liliemark is presented in table II.

The only commercially available form of cladribine is an intravenous injectable solution (1 mg/ml in normal sodium chloride and phosphate buffer),[26,27] but the kinetics of the drug have been tested after intravenous, oral, subcutaneous and rectal administration. Other solutions have been prepared for subcutaneous administration (buffered 2.5 mg/ml at pH 7.4) or oral use (isotonic 1 mg/ml),[22] and the drug has been formulated into enteric-coated capsules for oral testing.[28] Although the kinetics of the drug after oral and rectal administration have been examined in patients with malignancies[24] and the oral drug has been tested in clinical trials of patients with MS,[22] bioavailability of these 2 forms is low (≤51% oral; ≈20% rectal) and variable, so their use in patients with MS is not generally recommended (see section 5). Also, although originally used as a continuous 24-hour intravenous infusion, intravenous cladribine is now usually administered to patients with MS as 2-hour infusions once daily or as subcutaneous injections; these regimens/routes appear to result in pharmacokinetics and efficacy similar to those seen with use of the intravenous route.[24]

Table II. Overview of cladribine pharmacokinetic parameters in adult patients with haematological malignancies (data from the review by Liliemark[24] unless otherwise noted)

Parameter	Route		
	IV	SC	PO
F (%)		100	37-51
C_{max} (nmol/L)	142 after 2h 0.12 mg/kg infusion	268 after 0.12 mg/kg	165 after 0.24 mg/kg
$t_{½\alpha}$ (min)	8-11.9		
$t_{½\beta}$ (h)	0.7-1.5		
$t_{½\gamma}$ (h)	5.7-13.4		
V_{ss} (L/m^2)	54-368		
CL (L/h/m^2)	26-45		
CSF : plasma concentration ratio	0.25		
PB (%)[25]	Patients with haematological malignancies: 25 Healthy volunteers: 21.1 Human serum albumin *in vitro*: 24.3		

Abbreviations: CL = clearance; C_{max} = peak plasma concentration; F = bioavailability; IV = intravenous; PB = plasma protein binding; PO = oral; SC = subcutaneous; $t_{½\alpha}$ = distribution half-life; $t_{½\beta}$ = elimination half-life; $t_{½\gamma}$ = terminal elimination half-life; V_{ss} = volume of distribution at steady-state.

2.2.1 Absorption and Distribution

Having no local tissue toxicity and 100% bioavailability, cladribine is suitable for administration as a subcutaneous injection.[24] Variability in the area under the plasma concentration-time curve (AUC) is high between individuals, but is similar after oral and intravenous administration (coefficient of variation 38 *vs* 36%).[24] Oral cladribine has low (37 to 51%) bioavailability. Food slowed and reduced oral absorption of cladribine. Although cladribine is unstable at low pH, oral bioavailability was not substantially increased by raising stomach pH with omeprazole.[24]

Cladribine has a short distribution half-life of 8 to 11.9 hours and is widely distributed in the body cells, with a steady-state volume of distribution of up to 368 L/m^2. Concentrations of the drug and its nucleotides within cells are several hundred times higher than concentrations of the parent drug in plasma, but cannot be predicted by plasma concentrations. Cladribine and its metabolites are also retained in leukaemic cells, with a half-life of up to 30 hours, making the drug suitable for intermittent

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