
Cladribine in the treatment of hairy-cell leukaemia

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Cladribine, a purine nucleoside analogue, is a safe and effective treatment for patients with hairy-cell leukaemia. It is administered at a dose of 0.09 mg/kg daily as a continuous intravenous infusion over 7 days. This chapter discusses the history, rationale, chemical structure and mechanism of action of cladribine. The indications for therapy and guidelines for clinical usage are reviewed. The response of hairy-cell leukaemia to cladribine, the acute and chronic complications and the risk for second malignancies are summarized. The chapter concludes with a section on salvage therapy.

Key words: cladribine; 2-chlorodeoxyadenosine; hairy-cell leukaemia; purine analogue.

HISTORY AND RATIONALE

Cladribine (2-chlorodeoxyadenosine, 2-CdA, Leustatin[®], Ortho Biotech, Raritan, NJ, USA) is a purine nucleoside analogue resistant to deamination by the enzyme adenosine deaminase (ADA). It is active against both resting and dividing lymphoid cells. The application of cladribine to the treatment of lymphoproliferative disorders was a consequence of the work of Professor Dennis Carson. He had demonstrated that lymphocytes possessed particularly high levels of deoxycytidine kinase activity and low levels of the phosphatase. Because ADA provided the only pathway for

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degradation of deoxypurine nucleosides, he reasoned that ADA deficient cells would accumulate deoxypurine nucleotides¹, a prediction that was borne out by the studies of Donofrio et al.²

Thus, when a purine nucleoside analogue resistant to ADA is administered to patients, its nucleotide derivatives selectively accumulate in lymphocytes, producing cell death in much the same manner as is seen in ADA deficiency. Carson screened approximately 25 purine derivatives and chose cladribine because it had the most favourable therapeutic to toxicity ratio.³ Cladribine was synthesized by Carson et al from 2-chloroadenine and thymidine using transdeoxyribosylase from *Lactobacillus helveticus*.⁴ Commercially it is synthesized non-enzymatically using a sodium salt glycosylation procedure.⁵

PHYSIOLOGY, MECHANISM OF ACTION AND CHEMICAL STRUCTURE

Deoxypurine nucleosides are introduced into the intracellular milieu through a transport mechanism.³ Intracellularly, they are phosphorylated by deoxycytidine kinase into mononucleotides. ADA regulates the intracellular concentration of deoxyadenosine through the deamination of deoxyadenosine to deoxyinosine.

Cladribine is a deoxyadenosine analogue in which a chlorine atom has been substituted for the hydrogen atom at the 2-position of the purine ring (Figure 1). This substitution renders cladribine resistant to ADA. Thus, in lymphocytes, in which the activity of deoxycytidine kinase is high and 5'-nucleotidase activity is low, the administration of cladribine results in the accumulation of its nucleotides, which are incorporated into DNA³ (Figure 2). In addition, it has been postulated that the accumulation of abnormal concentrations of deoxyribonucleotides may initiate apoptosis.⁶ Seto et al⁷ found that lymphocyte DNA strand breaks occur within 4 hours after exposure to cladribine. The ends of the single strands of DNA activate

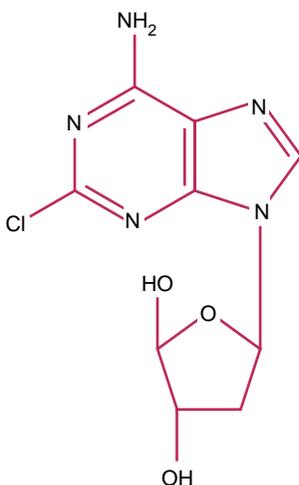


Figure 1. The structure of cladribine (2-CdA). The hydrogen atom at the 2-position of the purine ring has been substituted with a chlorine atom.

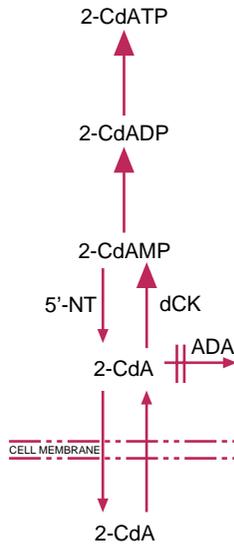


Figure 2. Cladribine (2-CdA): mechanism of action. Cladribine is transported into the cell. It resists deamination by adenosine deaminase (ADA). The high ratio of deoxycytidine kinase (dCK) to 5'-nucleotidase (5'-NT) favours the formation of 2-chlorodeoxyadenosine monophosphate (2-CdAMP), 2-chlorodeoxyadenosine diphosphate (2-CdADP) and 2-chlorodeoxyadenosine triphosphate (2-CdATP).

a poly(ADP-ribose) synthetase with the resultant consumption of cellular nicotinamide adenine dinucleotide (NAD). This leads to cell death because cells cannot perform metabolic functions in the absence of NAD.

INDICATIONS FOR THERAPY

Cladribine is approved by the Food and Drug Administration in the USA for the treatment of active hairy-cell leukaemia (significant anaemia, neutropenia, thrombocytopenia or disease-related symptoms).⁸ It also has activity in chronic lymphocytic leukaemia (CLL)^{9–12}, non-Hodgkin lymphoma^{11,13,14}, Waldenström macroglobulinaemia¹⁵, cutaneous T-cell lymphoma¹⁶, acute myelogenous leukaemia^{11,17,18}, and chronic myelogenous leukaemia.^{18,19} Small numbers of patients with astrocytomas²⁰, Hodgkin disease¹¹, Coombs-positive autoimmune haemolytic anaemia unrelated to a lymphoproliferative disorder¹¹, and Langerhans cell histiocytosis²¹ have responded to single-agent cladribine administration. In addition, cladribine has been used in the treatment of multiple sclerosis^{22,23}, psoriasis²⁴ and lupus nephritis.²⁵

When patients with hairy-cell leukaemia are asymptomatic and significant cytopenias are absent, watchful waiting is appropriate because early treatment confers neither a survival nor response benefit. Treatment of hairy-cell leukaemia should be considered for symptomatic patients. Treatment is indicated for patients with significant neutropenia (absolute neutrophil count less than $1 \times 10^9/l$), anaemia (haemoglobin concentration less than 10.0 g/dl), thrombocytopenia (platelets less than $100 \times 10^9/l$), symptomatic splenomegaly, constitutional symptoms due to hairy-cell leukaemia (fevers

or night sweats), or recurrent serious infections. Other indications for treatment include leukocytosis with a high proportion of hairy-cells (white cell count greater than $20 \times 10^9/l$), bulky or painful lymphadenopathy, vasculitis and bony involvement.

Many effective therapies exist for the treatment of hairy-cell leukaemia. Besides cladribine, which is the focus of this chapter, pentostatin, interferon- α , splenectomy, rituximab (mabthera), fludarabine, BL22 immunotoxin and irradiation of bony lesions have been used in the treatment of hairy-cell leukaemia.

GUIDELINES FOR CLINICAL USAGE AND ADMINISTRATION OF CLADRIBINE

Cladribine is administered by a continuous intravenous infusion at a dose of 0.09 mg/kg in 500 ml 0.9% sodium chloride daily over a 7-day period.⁸

Alternative methods of administration have been investigated. A 2-hour bolus administration of cladribine given daily for 5 consecutive days was assessed by Saven and colleagues in patients with CLL.²⁶ This was developed in an attempt to facilitate the outpatient administration of cladribine. Ninety alkylator-failed CLL patients were treated (21 with bolus cladribine and 89 with continuous infusion cladribine). Cladribine at a dose 0.14 mg/kg daily by 2-hour intravenous bolus infusion had similar response rates and toxicities compared to cladribine given at 0.1 mg/kg daily by continuous infusion over 7 days.

Lauria et al²⁷ described the treatment of 25 hairy-cell leukaemia patients treated with cladribine at a dose of 0.15 mg/kg weekly for 6 weeks. Seventy-six percent of patients achieved a complete response and 24% a partial response. The median disease-free survival was 14.7 months. Two patients, who had achieved a partial response, had progression. Sixteen percent developed grade 4 neutropenia (absolute neutrophil count less than $0.5 \times 10^9/l$) and 8% developed an infectious episode.

The oral bioavailability of cladribine was first studied by Liliemark et al.²⁸ They estimated the oral bioavailability of cladribine at 48% when given at 0.14 mg/kg daily for 5 days and 55% when given at 0.28 mg/kg daily for 5 days. Saven et al²⁹ performed a separate study. In cycle 1, 10 patients received oral cladribine at a dose of 0.28 mg/kg daily for 5 consecutive days; cladribine (1.0 mg/ml) was given after an overnight fast. Patients swished for 20 seconds and then swallowed the cladribine solution. This was followed by 50–100 ml of water. In addition, patients were treated with omeprazole 20 mg/kg for 5 days 2 hours before receiving oral cladribine. This was performed because it is believed that cladribine is unstable in an acid environment. Four weeks later, in cycle 2 of the study, patients received cladribine at 0.14 mg daily intravenously, over 2 hours for 5 consecutive days. The oral bioavailability of cladribine was approximately 37% and there were no cumulative differences in bioavailability observed on multiple dosing. Thus the oral bioavailability of cladribine is between 37 and 55% and can be effectively administered at approximately double the intravenous dose.

Liliemark and colleagues²⁸ treated ten patients on alternate days with cladribine at 0.14 mg/kg daily as a 2-hour intravenous infusion or by subcutaneous injection. A high-performance liquid chromatography method was used for the analysis of plasma cladribine concentrations. The bioavailability of subcutaneous cladribine was determined to be 100% and no local toxicity was noted.

The optimum route and method of administration for cladribine remains to be clarified. The weekly and bolus intravenous, subcutaneous and oral methods remain to

be tested in large numbers of patients, and longer follow-up is needed to determine whether these methods of delivery are equivalent to the 7-day continuous intravenous infusion method.

RESPONSES WITH AND RELAPSES FOLLOWING CLADRIBINE

The first documentation of the profound activity of cladribine in the treatment of hairy-cell leukaemia was made in 1987 by Carrera et al.³⁰ In 1990, investigators at Scripps Clinic reported on 12 hairy-cell leukaemia patients treated with a single 7-day continuous intravenous infusion of cladribine at 0.085 mg/kg daily; 11 achieved a complete response and one achieved a partial response.³¹

In 1998, Saven et al.³² reported the follow-up of 358 hairy-cell leukaemia patients treated with cladribine. Of the 349 evaluable patients, 91% achieved an initial complete response and 7% a partial response with an overall median duration of response follow-up of 52 months. Of the 22 patients who achieved a partial response, 14 had no clinical evidence of splenomegaly and had peripheral blood counts within the normal reference range; however, they were found to have residual disease on bone marrow biopsy. In addition, three partial responders had residual disease in the bone marrow associated with splenomegaly and peripheral cytopenias. Twenty-six percent of patients relapsed at a median of 29 months. Of the 53 evaluable hairy-cell leukaemia patients treated with a second course of cladribine, 62% achieved a complete response and 26% a partial response. The overall survival was 96% at 48 months. The time-to-treatment failure rate for complete responders was 16.3% at 4 years.

Goodman et al.³³ recently reviewed the outcome data of 209 Scripps Clinic hairy-cell leukaemia patients who had at least seven years of follow-up. Patients again received cladribine as a 7-day continuous intravenous infusion at a dose of 0.085–0.1 mg/kg daily. Of the 207 evaluable patients, 196 (95%) achieved a complete response and 11 patients (5%) a partial response following a single course of cladribine; thus the overall response rate was 100%. The median first response duration for all responders was 98 months. Patients who achieved a complete response had a median first response duration of 99 months, and patients who had achieved a partial response had a median first response duration of 37 months. Seventy-six (37%) patients relapsed after their first course of cladribine. Of these, 67 patients (88%) had achieved a prior complete response, and nine patients (12%) a prior partial response. The median time to first relapse for all responders was 42 months. Patients who had achieved a prior complete response had a median time to first relapse of 44 months, and patients who had achieved a prior partial response had a median time to first relapse of 31 months. Time-to-treatment failure for the complete responders, compared to partial responders, was statistically significant. There was no obvious plateau on the time-to-treatment failure curve; thus, it is unclear as to what proportion of patients, if any, will be cured.

It has been shown that 25–50% of patients in morphological complete remission after treatment with cladribine have minimal residual disease demonstrated by immunohistochemistry of bone marrow specimens.^{34,35} In addition, Filleul et al demonstrated that seven hairy-cell leukaemia patients in apparent complete remission had minimal residual disease detected by polymerase chain reaction and clonogenic probes derived from the immunoglobulin heavy-chain genes.³⁶

In the above study by Goodman et al³³ 60 patients (79%) received a second course of cladribine after relapsing. Of the 59 evaluable patients, 44 (75%) achieved complete

responses and 10 (17%) partial responses, while 5 (8%) failed to respond. The median second response duration for all responders was 35 months.

Twenty patients (33%) suffered a second relapse. Of these patients, 10 (50%) received a third course of cladribine; six patients achieved a complete response, two patients achieved a partial response, one patient had no response and one patient was unevaluable because neither bone marrow biopsy nor blood parameters were available for review. The median third response duration for all responders was 20 months.

Two patients received a fourth course of cladribine. One patient achieved a complete response and the other was unevaluable because neither bone marrow biopsy nor blood parameters were available for review. The response duration for this single patient was 42 months (censored at last follow-up).

Of the 209 patients who had at least 7 years of follow-up, six (3%) patients have died (all complete responders). The causes of death in these patients were hairy-cell leukaemia and a diverticular abscess (after rituximab) (one patient), acute myocardial infarction (one patient), Alzheimer's disease/multi-infarct dementia (one patient), metastatic prostate cancer (one patient) and unknown (two patients; details of death unavailable for review). The overall survival was 97% recorded at 108 months.

Hoffman et al³⁷ described the experience of the Long Island Jewish Medical Center, New York, USA, with 49 hairy-cell leukaemia patients treated with cladribine. The initial complete response rate was 76% and the partial response rate 24% (overall response rate 100%). The median follow-up was 55 months. The relapse-free survival was 80% and the overall survival was 95%. Two patients died. One patient died from an adenocarcinoma of unknown primary and the other died of a dementing illness of unknown cause, 34 and 21 months, respectively, after receiving cladribine. Five second malignancies were noted in four patients. One patient developed localized gastric large-cell lymphoma and later developed metastatic adenocarcinoma of unknown primary. Two patients developed localized prostate adenocarcinoma and one patient developed a localized superficial transitional cell carcinoma of the bladder.

Tallman et al³⁸ reported on the Northwestern University, Chicago, Illinois, USA, data where 52 patients received a single course of cladribine and had a median follow-up of 33 months. Fifty patients were evaluable. The complete response rate was 80% and the partial response rate 18%. Two percent of patients failed to respond initially but had achieved a complete response by 6 months. The relapse rate was 14%. The estimated progression-free survival was 72% at 4 years. The overall survival was 86% at 4 years. Four patients died (two patients of progressive hairy-cell leukaemia, one patient from an unrelated cardiac event and the other patient died of a ruptured abdominal aortic aneurysm). There was one reported second malignancy (prostate cancer).

Cheson et al³⁹ described the National Cancer Institute's (USA) Group C Protocol results in 979 patients treated with cladribine. There were 861 evaluable patients, 50% achieved a complete response, 13% achieved a good partial response and 24% achieved a partial response. The overall response rate was 87%. The reason for the much lower complete response rate reported in this study is unclear but may have been related to the absence of central pathology review. The median follow-up duration for surviving patients was 52 months. The median disease-free survival, median time to progression and the median survival time had not been reached. Of the 928 patients available for review, there were 125 deaths—50% due to hairy-cell leukaemia, 18% due to other malignancies, 12% due to infection, 11% due to cardiac events, 2% due to cerebrovascular accidents and 6% due to other causes.

Table 1. Response rates seen in hairy-cell leukaemia patients treated with a single course of cladribine.

Institution	Number of evaluable patients	Complete response rate (%)	Partial response rate (%)	Overall response rate (%)
National Cancer Institute (USA) ³⁹	861	50	37	87
Scripps Clinic ^{32,a}	349	91	7	98
Scripps Clinic ^{33,b}	207	95	5	100
Northwestern University ³⁸	50	80	18	98
Long Island Jewish Medical Center ³⁷	49	76	24	100
M.D. Anderson Cancer Center ⁷⁴	46	78	11	89
Royal Marsden Hospital ⁷⁵	45	84	16	100
Huddinge and Karolinska Hospitals ⁷⁶	16	75	0	75

^a All patients treated with cladribine at Scripps Clinic, La Jolla, California, U.S.A.
^b Patients with greater than 7 years of follow-up.

Table 1 summarizes the response rates seen in hairy-cell leukaemia patients treated with a single course of cladribine.

USE OF GROWTH FACTORS IN COMBINATION WITH CLADRIBINE

Fever was the major acute toxicity occurring in 42% of patients in the Scripps Clinic study.³² Three hundred and forty-nine evaluable hairy-cell leukaemia patients were treated with a single course of cladribine at 0.085–0.1 mg/kg daily by continuous infusion for 7 days. Seventy-one percent of patients experienced grade 4 neutropenia (absolute neutrophil count less than $0.5 \times 10^9/l$). These patients with fever often appeared ill, with chills, headaches, myalgias, anorexia and malaise. This frequently resulted in hospitalization. Only 13% of patients had documented infections (viral or bacterial). No fungal infections were noted. Patients were treated with broad-spectrum antibiotics. The fever often responded to antipyretics and had generally defervesced within 3 to 5 days.

In 1999, Saven et al⁴⁰ published a study investigating the role of filgrastim (granulocyte colony stimulating factor, G-CSF) in the prevention of cladribine-induced neutropenic fever in hairy-cell leukaemia patients treated with cladribine. These patients were compared to well matched historic controls. Thirty-five patients were treated as outpatients and received cladribine at a dose of 0.1 mg/kg daily by continuous intravenous infusion for 7 days. Filgrastim was administered by subcutaneous injection at a dose of 5 µg/kg daily on days -3, -2, and -1 and after the completion of cladribine (day +8 onwards) until the absolute neutrophil count exceeded $2.0 \times 10^9/l$ on 2 consecutive days. If the absolute neutrophil count decreased to less than $1.0 \times 10^9/l$ after the filgrastim was discontinued, then filgrastim

was re-instituted until the absolute neutrophil count was again above $2.0 \times 10^9/l$. When neutropenic fever occurred, patients were hospitalized to exclude infection and to receive broad-spectrum intravenous antibiotics. Acetaminophen was used to treat temperatures greater than 38.5°C .

It was found that priming with filgrastim increased the neutrophil count without stimulating the number of circulating hairy cells. The median nadir absolute neutrophil count in the filgrastim-treated patients was statistically greater than that of the historic control patients ($0.53 \times 10^9/l$ versus $0.29 \times 10^9/l$). The time for the absolute neutrophil count to exceed $1.0 \times 10^9/l$ decreased from 22 to 9 days in the filgrastim-treated group. However, the number of febrile days (1 day versus 3 days; $P = 0.21$), the duration of fever in febrile patients (3 days versus 6 days; $P = 0.17$), the number of patients hospitalized (31% versus 43%; $P = 0.31$) and the number of hospital days (9 versus 7; $P = 0.44$) were not statistically different. This phase II study failed to detect any clinical advantage from the use of filgrastim with cladribine in the treatment of hairy-cell leukaemia. These investigators concluded that the routine use of filgrastim as an adjunct to cladribine could not be routinely recommended in hairy-cell leukaemia patients.

Juliusson et al⁴¹ treated 12 hairy-cell leukaemia patients undergoing cladribine therapy with granulocyte-macrophage colony stimulating factor (GM-CSF) ($400 \mu\text{g}$ daily) on days 1–21. GM-CSF did not improve neutropaenia or febrile events.

ACUTE COMPLICATIONS

In the initial dose-escalation studies performed by Beutler³, it was discovered that doses of cladribine in excess of 0.26 mg/kg daily for 10–14 days given to bone marrow transplant patients caused myelosuppression as well as severe renal and central nervous system toxicities. Several patients were placed on haemodialysis, and renal function returned to baseline in those patients who survived the complications of bone marrow transplantation. At a dose of 0.085 mg/kg daily, clinically significant nausea, vomiting, alopecia, nephrotoxicity, hepatotoxicity, pulmonary and cardiac toxicity and neurotoxicity have not been observed.⁵

Saven et al³² reported on the acute complications occurring in hairy-cell leukaemia patients after treatment with cladribine at a dose of 0.085 – 0.1 mg/kg daily by continuous intravenous infusion over 7 days. Of the first 135 consecutive patients treated, 16% developed grade-3 neutropenia (absolute neutrophil count between $0.5 \times 10^9/l$ and $1.0 \times 10^9/l$) and 71% developed grade 4 neutropenia (absolute neutrophil count less than $0.5 \times 10^9/l$). Ten percent developed grade 3 thrombocytopenia (platelet count between $25 \times 10^9/l$ and $50 \times 10^9/l$) and a further 10% had grade 4 thrombocytopenia (platelet count less than $25 \times 10^9/l$). Grade 3 anaemia (haemoglobin less than 8 g/dl) occurred in 20%, and grade 4 anaemia (haemoglobin less than 6.5 g/dl) occurred in 2% of patients. The median time to recovery of the peripheral blood counts after the first infusion of cladribine was 49 days and after the second infusion (in those patients who were re-treated with cladribine) it was 45 days.

Fever (temperature greater than 38.5°C) occurred in 42% of the 358 patients treated, while only 13% had documented infections. The following infections were noted: oral herpes simplex (five patients), herpes zoster (two patients with dermatomal zoster and one patient with disseminated zoster), acute cytomegalovirus retinitis (one patient), staphylococcal bacteraemia (10 patients), *Staphylococcus* was also cultured from cellulitis or from the catheter tip (23 patients), β -haemolytic

streptococcus (one patient), *Streptococcus pneumoniae* (one patient), *Escherichia coli* (one patient), micrococci bacteraemia (one patient), *Branhamella catarrhalis* (one patient). Three patients had urinary tract infections (*Escherichia coli*, Gram-positive cocci not further identified and coagulase-negative *Staphylococcus*). There were no acute fungal infections.

One patient had an acute splenic rupture midway through his first cladribine infusion and underwent an emergency splenectomy. A single patient developed transient chylous ascites. Cardiac arrhythmias were seen in two patients (one paroxysmal atrial tachycardia and one ventricular tachycardia).

LONG-TERM COMPLICATIONS

Scripps Clinic investigators³² reported on the delayed complications occurring in hairy-cell leukaemia patients after treatment with cladribine at a dose of 0.085–0.1 mg/kg daily by continuous intravenous infusion over 7 days.

Infections were the most common delayed complication. Dermatomal herpes zoster occurred in seven patients, hepatitis C in two patients (both had received prior transfusions), and *Mycobacterium tuberculosis* and *Mycobacterium chelonae* were documented in single patients.

Other delayed complications reported with an unclear relationship to cladribine were myocardial infarction (one patient), stroke (one patient), interstitial lung disease (one patient), pulmonary embolism (one patient), peripheral neuropathy (two patients), transverse myelitis (one patient), thyrotoxicosis (two patients), psoriatic arthropathy (one patient) and polymyalgia rheumatica (one patient).

Immunosuppression, as evidenced by lymphocyte subset analysis, is present for approximately 6–12 months following a single course of cladribine.^{3,5} However, reduction in CD4⁺ populations has been reported to extend for up to 40 months.⁴² Cladribine has been shown to reduce the number of both B and T lymphocytes. A decrease in the CD4⁺/CD8⁺ ratio due to slower recovery of the CD4⁺ lymphocytes has been observed.⁵ In addition, immunosuppression is probably enhanced by inhibition of lymphocyte activation. Inhibition of both B and T lymphocytes has been documented *in vitro*.^{43,44} The lymphocyte immunosuppression observed following cladribine therapy might account for the slight increase in early and late infections seen in patients treated with cladribine.

SECOND MALIGNANCIES

The risk of second malignancies occurring in hairy-cell leukaemia patients after treatment with cladribine at a dose of 0.085–0.1 mg/kg daily by continuous intravenous infusion over 7 days has been reported. Goodman et al³³ analysed second malignancies in 379 hairy-cell leukaemia patients. Forty-seven patients (22%) developed 58 second malignancies; these are summarized in Table 2. Only three patients developed a haematological malignancy following cladribine therapy. The observed-to-expected ratio of developing a second malignancy, as compared to NCI SEER data⁴⁵, was 2.03 (95% CI: 1.49–2.71). Further analysis using logistic regression to model the risk of second malignancies revealed that the older the patient, the more likely was the occurrence of a second malignancy (2.45-fold greater for individuals in successive age

Table 2. The incidence of second malignancies in 379 patients treated with cladribine at Scripps Clinic, La Jolla, CA, USA.

	Number of patients	Number of second malignancies
Non-Hodgkin lymphoma	3	3
Non-melanoma skin cancer	17	20
Melanoma	3	3
Prostate	14	14
Colon	6	6
Stomach	3	3
Renal	2	2
Bladder	1	1
Breast	2	3
Brain	1	1
Liver	1	1
Unknown primary	1	1

Note: 38 patients had a single second malignancy, eight patients had two, and one patient had four second malignancies.

quartiles, 95% CI: 1.45–4.14) and that patients who had had a malignancy prior to the diagnosis of hairy-cell leukaemia had a 3.7-fold increased risk of developing an additional malignancy compared to those who did not (95% CI: 1.33–10.31). This suggests that factors other than cladribine itself had contributed to the risk of a developing a second malignancy. It has been suggested that the impairment in natural-killer cell and T-cell function documented following cladribine in hairy-cell leukaemia patients may play a role in the formation of second malignancies.^{42,46–48} However, in a study by Cheson et al⁴⁸, the authors did not find an additional risk of second malignancies in hairy-cell leukaemia patients treated with either cladribine or pentostatin.

The percentage of hairy-cell leukaemia patients who develop second malignancies has varied widely. It has been recorded to be as high as 31% in a study by Au et al who described the 20-year experience in British Columbia, Canada.⁴⁹ In this study of 117 patients (90 men and 27 women), 36 patients developed a total of 44 separate additional malignancies. In contrast, Kurzrock et al⁵⁰ reported on the M.D. Anderson (Houston, Texas, USA) experience of 350 hairy-cell leukaemia patients treated since 1968. There were 285 men and 65 women, the median age was 50 years and the mean follow-up time after diagnosis was 7.1 years. Twenty-six patients (7.4%) developed a total of 31 malignancies. There was no statistically significant increase in second malignancies in hairy-cell leukaemia patients as compared to data derived from the Connecticut Tumor Registry. Overall, it is thought that the risk of second malignancies in hairy-cell leukaemia patients is related to disease burden and not to treatment.

SALVAGE TREATMENTS FOLLOWING CLADRIBINE

Pentostatin

Pentostatin (Nipent[®], SuperGen Inc., Pleasanton, CA, U.S.A.) is a tight-binding inhibitor of ADA and hence simulates genetic ADA deficiency, thereby leading to lymphocyte death.⁵¹

Pentostatin is given at a dose of 4 mg per square-metre every other week for 3–6 months to maximal response. Adverse effects from pentostatin include fever, nausea, vomiting, photosensitivity and keratoconjunctivitis.^{52,53} It is immunosuppressive, and patients with poor bone marrow reserve are at greatest risk.^{54,55} Pentostatin is intensely immunosuppressive, even at low doses.^{56,57} Infectious complications that have been observed after pentostatin therapy include disseminated herpes zoster, *Escherichia coli*, *Haemophilus influenzae*, pneumococcal and fungal infections.⁵³ Pentostatin should probably not be used in patients with active or uncontrolled infections, a poor performance status, or renal dysfunction (creatinine clearance less than 60 ml/minute).^{54,58}

There appears to be a lack of cross-resistance between cladribine and pentostatin despite structural and mechanistic similarities. There are reports of patients who have responded to pentostatin after having relapsed after cladribine therapy, and vice versa.^{32,59} In a study by Saven et al³² 358 hairy-cell leukaemia patients were treated with cladribine; of seven patients salvaged with pentostatin following relapse, three had complete responses, three partial responses and one patient failed to respond.

Pentostatin may represent a reasonable salvage therapy in selected hairy-cell leukaemia patients who have failed cladribine; however, there is a paucity of data reflecting the response rates and duration of response in large numbers of patients. Direct comparisons cannot be made between the pentostatin and cladribine trials due to differences in study design. No head-to-head randomized trials have thus far been performed.

Interferon-alpha

Interferon- α induces partial responses in most hairy-cell leukaemia patients but complete responses in only a minority of patients.⁶⁰ It is useful in the treatment of hairy-cell leukaemia patients who present with active infections and are therefore unable to undergo purine nucleoside analogue therapy due to the resultant T-cell immunosuppression.^{57,61} Interferon- α is also useful in patients who have failed purine analogue therapy.⁶² A recent in vitro study⁶³ showed that therapeutic concentrations of interferon- α induced apoptosis of non-adherent hairy cells by increasing the secretion of tumour necrosis factor- α and the sensitization of hairy cells to the pro-apoptotic effect of autocrine tumour necrosis factor- α .

Interferon- α -2b (Intron A[®], Schering Corporation, Kenilworth, NJ, USA) is given at a dose of 2 million units per square-metre by subcutaneous injection three times a week for 12 months. Interferon- α -2a (Roferon A[®], Roche Laboratories, Nutley, NJ, USA) is initially given at a dose of 3 million units per square-metre by subcutaneous injection daily for 6 months and then decreased to three times per week for an additional 6 months.

Side-effects of interferon- α include a flu-like syndrome (fever, myalgias and malaise). Acetaminophen can be used to ameliorate these symptoms, and tachyphylaxis usually develops over time.

In a study by Saven et al³² 358 hairy-cell leukaemia patients were treated with cladribine. A total of nine patients were given salvage treatment with interferon- α following relapse. Of these nine patients, there was one complete response, two partial responses and six patients did not respond.

Seymour and colleagues⁶² treated 46 hairy-cell leukaemia patients with cladribine. Forty-one patients responded; of these, eight patients relapsed. Three of these patients were treated with interferon- α and all three had an objective response, which was

maintained while receiving interferon- α . However, two patients relapsed after discontinuation of interferon- α .

Splenectomy

Current indications for splenectomy include active or uncontrolled infections, bleeding associated with severe thrombocytopenia, massive painful or ruptured splenomegaly and failure of chemotherapy, including cladribine. Response to splenectomy is not uniform, because cytopenias may be due to diffuse bone marrow infiltration by hairy-cell leukaemia rather than principally hypersplenism from splenic enlargement.⁶⁴

In a Scripps Clinic study³², 358 hairy-cell leukaemia patients were treated with cladribine; eight patients did not respond, and of these, one patient underwent a splenectomy with a resultant improvement in peripheral blood cytopenias. Of 341 patients who initially responded to cladribine, 90 relapsed and two of these patients underwent splenectomy without benefit.

Rituximab (Mabthera)

Hairy cells express the pan B-cell antigens, including CD20.^{65–67} Rituximab (Rituxan[®], IDEC Pharmaceuticals, San Diego, CA, USA), a monoclonal antibody targeting CD20, has been studied in refractory or relapsed hairy-cell leukaemia. Thomas et al⁶⁸ reported on a study at the M.D. Anderson cancer center, Houston, Texas, USA, in which rituximab was used in eight refractory hairy-cell leukaemia patients. Of the five evaluable patients, four responded (two complete responses, one complete response with minimal residual disease, and one partial response). The toxicity reported was limited to rigors associated with the rituximab infusion in seven of the eight patients. Nieva et al⁶⁹ from the Scripps Clinic reported on a phase II study of rituximab in cladribine-failed hairy-cell leukaemia patients. Of 15 evaluable patients, there were two complete responses, one complete response with minimal residual disease, and two partial responses. Rituximab therapy was well tolerated.

Fludarabine

Fludarabine (Fludara[®], Berlex Laboratories, Richmond, CA, USA) has been used only sparingly in the treatment of hairy-cell leukaemia. The response rates are lower than that produced by cladribine but may be marginally higher in hairy-cell leukaemia variants.^{70–72} No studies, thus far, have been reported documenting the potential activity of this purine analogue in cladribine-failed patients.

BL-22 immunotoxin

Kreitman et al⁷³, in a recent article, demonstrated the efficacy of a recombinant immunotoxin BL22 in the treatment of hairy-cell leukaemia. BL22 contains the variable domain of an anti-CD22 monoclonal antibody fused to a fragment of a pseudomonas exotoxin. In this small study of 16 'cladribine-resistant' patients, 11 achieved a complete response and two a partial response. Two patients developed reversible haemolytic-uraemic syndrome. Although BL22 represents an exciting new approach to the treatment of this disease, these results need to be interpreted cautiously given the potential life-threatening toxicity of this agent.

SUMMARY

Cladribine is a purine nucleoside analogue resistant to deamination by the enzyme ADA. It is a safe and effective treatment for patients with hairy-cell leukaemia. It is given at a dose of 0.09 mg/kg daily as a continuous intravenous infusion over 7 days. Treatment of hairy-cell leukaemia should be considered for symptomatic patients. Treatment is indicated for patients with significant neutropenia, anaemia, thrombocytopenia, symptomatic splenomegaly, constitutional symptoms due to hairy-cell leukaemia (fevers or night sweats), or recurrent serious infections. The majority of patients enjoy long-lasting complete remissions and those patients who relapse can frequently be re-treated successfully with cladribine.

Practice points

- cladribine is a safe and effective treatment for hairy-cell leukaemia patients
- indications for treatment include significant neutropaenia, leukocytosis with a high proportion of hairy-cells, anaemia, thrombocytopenia, symptomatic splenomegaly, constitutional symptoms due to hairy-cell leukaemia, recurrent serious infections, bulky or painful lymphadenopathy, vasculitis and bony involvement
- watchful waiting is appropriate for asymptomatic patients who do not have significant cytopenias
- cladribine is administered by a continuous intravenous infusion at a dose of 0.09 mg/kg in 500 ml 0.9% sodium chloride daily over a 7-day period
- in cladribine naïve hairy-cell leukaemia patients, a single course of cladribine produces an overall response rate of 75–100% and a complete response rate of 50–95%
- the majority of hairy-cell leukaemia patients treated with cladribine enjoy long-lasting complete remissions, and those patients who relapse can frequently be re-treated successfully with cladribine. Additional salvage therapies include pentostatin, interferon- α , splenectomy, rituximab (mabthera) and BL-22 immunotoxin

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