

Original Article

Cladribine Treatment in Two-Hour Intravenous Infusion for Previously-Treated Low Grade B-Cell Lymphoma : A Pilot Study

Yasushi Takamatsu,¹⁾ Junji Suzumiya,^{1,2)} Kentaro Ogata,³⁾ Keiko Katayose,^{1,4)}
Hidenori Sasaki,¹⁾ Kenji Ishitsuka,¹⁾ Nobuhiro Kimura,¹⁾ and Kazuo Tamura¹⁾

Cladribine is approved to be used in 24-hour continuous infusion for the treatment of low-grade lymphoma by the Ministry of Health, Labor and Welfare in Japan. Pharmacokinetic studies showed that the antitumor activity of cladribine by 2-hour infusion should be comparable to that given by continuous infusion. The safety and anti-tumor activity of short infusion of cladribine was shown in hairy cell leukemia, chronic lymphocytic leukemia and low-grade non-Hodgkin's lymphoma in Europe. We therefore underwent a pilot study to confirm the safety and efficacy of cladribine given by 2-hour infusion for Japanese patients with relapsed or refractory indolent B-cell lymphoma. Cladribine at a dose of 0.09 mg/kg was administered in 2-hour intravenous infusion for 5 consecutive days. The treatment was repeated at a 28-day interval for at least 2 cycles, and its efficacy and toxicity were investigated. Fourteen patients were entered into this study. Eight patients (57%) responded to cladribine, including 2 (14%) complete response (CR) and 6 (43%) partial response (PR). The median duration of response was 20+ and 21+ months for CR, and 12 months ranging from 3 to 34 months for PR, respectively. Grade 3 or 4 neutropenia and lymphocytopenia occurred in 43% and 71% of patients, respectively, but there was no febrile neutropenia or opportunistic infection associated with cladribine treatment. No other adverse events greater than grade 3 were encountered. The tumor response and degree of toxicity were comparable with those observed in cladribine treatment given by continuous infusion at a same dose. Cladribine can be administered in 2-hour infusion in an outpatient clinic and is therefore quite convenient for patients. [*J Clin Exp Hematopathol* 49(2) : 69-75, 2009]

Keywords: low-grade B-cell lymphoma, cladribine, 2-hour infusion

INTRODUCTION

Cladribine is a purine analogue that is resistant to degradation by adenosine deaminase. It is phosphorylated by deoxycytidine kinase and accumulates intracellularly as a nucleoside triphosphate. Since levels of deoxycytidine kinase are higher in normal and malignant lymphoid cells than in other tissues, this agent is markedly toxic to normal lympho-

cytes as well as lymphoid malignancies.¹ Cladribine rapidly induced DNA strand breaks,² followed by a progressive decrease in RNA synthesis, accelerated consumption of nicotinamide adenine dinucleotide and decline in adenosine 5'-triphosphate levels, leading to subsequent programmed cell death *in vitro*. Unlike conventional antimetabolites that impede nucleic acid synthesis in proliferating cells, cladribine is extremely toxic to both dividing and resting cells.³ Cladribine has therefore clinical activity against indolent lymphoid tumors including hairy cell leukemia, chronic lymphocytic leukemia and low-grade non-Hodgkin's lymphoma.

A phase II study for cladribine was conducted at a dose of 0.09 mg/kg daily as a continuous intravenous infusion over 7 days in Japan. Pharmacokinetic study showed a long terminal half-life of cladribine following a 2-hour infusion. The area under the time versus concentration curves (AUC) for the 2-hour infusion was similar to those of continuous infusion.⁴ Moreover, in patients with lymphoid leukemia, no significant difference was observed in the intracellular concentration of cladribine nucleotides between 2 modes of administration.⁵

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¹⁾ Division of Medical Oncology, Hematology and Infectious Disease, Department of Medicine, Fukuoka University Hospital, Fukuoka, Japan

²⁾ Second Department of Internal Medicine, Fukuoka University Chikushi Hospital, Fukuoka, Japan

³⁾ Department of Pharmacology, Fukuoka University Hospital, Fukuoka, Japan

⁴⁾ Second Department of Internal Medicine, Miyazaki University, Miyazaki, Japan

Address correspondence and reprint request to Yasushi Takamatsu, M.D., Ph.D., Division of Medical Oncology and Hematology, Department of Medicine, Fukuoka University Hospital, 7-45-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan

E-mail : yasushi@fukuoka-u.ac.jp

The data indicate that the anti-tumor activity of 2-hour infusion of cladribine should be as strong as that given by continuous infusion. The safety and anti-tumor activity of short infusion of cladribine was shown in hairy cell leukemia, chronic lymphocytic leukemia and low-grade non-Hodgkin's lymphoma in Europe.⁶⁻¹⁰ We, therefore, underwent a pilot study of cladribine treatment in 2-hour intravenous infusion for Japanese patients with relapsed or refractory indolent B-cell lymphoma.

PATIENTS AND METHODS

Patients

All patients with relapsed or refractory indolent B-cell lymphoma were consecutively enrolled in this study during the period of March 2005 and April 2007. Histological diagnosis was established according to the World Health Organization (WHO) classification and the definition of low-grade (indolent) lymphoma was based on the classification previously described.¹¹ Eligibility criteria were as follows: age older than 20 years, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 3; adequate hematological parameters, i.e. neutrophil counts $\geq 1.5 \times 10^9/L$, and platelet counts $\geq 75 \times 10^9/L$, adequate renal function, serum creatinine ≤ 3 times the upper normal limit, adequate hepatic function, serum total bilirubin ≤ 3 times the upper normal limit, and aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≤ 5 times the upper normal limit; and normal electrocardiogram. Exclusion criteria included active concurrent malignancies, active systemic infection, positive results for hepatitis B virus surface antigen, or other serious medical or psychiatric conditions. Informed consent was obtained from all patients.

Cladribine treatment regimen

Cladribine was administered at a dose of 0.09 mg/kg daily in 2-hour intravenous infusion for 5 consecutive days. The treatment was to repeat at a 28-day interval for at least 2 cycles. When complete or partial response was obtained, cladribine was withheld and no further chemotherapy was given until disease progression was observed. If disease progression was observed after 2 cycles, the treatment was discontinued. All patients received oral trimethoprim-sulfamethoxazole for *Pneumocystis jiroveci* pneumonia as a prophylaxis. The treatment protocol was approved by the Institutional Review Board of Fukuoka University Hospital.

Response and toxicity criteria

Tumor response was assessed according to WHO criteria. Complete response (CR) was defined as a complete disap-

pearance of clinical and radiological evidence of lymphoma, lasting for at least 4 weeks. Partial response (PR) was defined as reduction in size of all tumors by at least 50%, lasting for at least 4 weeks. Progressive disease (PD) was defined as development of new lesions or a 25% or more increase in size. Any tumor response between PR and PD was defined as stable disease (SD).

Hematological and non-hematological toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria version 3.0.

A primary endpoint of this study is to evaluate the overall response rate of cladribin in 2-hour intravenous infusion. We also investigated the safety of the treatment as a secondary endpoint.

RESULTS

Patient population

Fourteen patients aged from 44 to 77 years (median; 61) were entered into this study. Five patients were male and nine were female. Twelve patients had follicular lymphoma, 1 had small lymphocytic lymphoma, and 1 had marginal zone lymphoma. The median number of previous regimens was 2 (range; 1-4). All but one patient had received CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisolone) with rituximab. One patient was previously treated with rituximab alone. No patient had undergone either autologous or allogeneic hematopoietic stem cell transplantation. Thirteen patients had recurred after prior anti-lymphoma therapy and 1 patient had progression of the disease on initial rituximab-combined CHOP therapy. The patients' characteristics are shown in Table 1.

Response and survival

Eight of 14 patients (57%) responded to the cladribine therapy. Two (14%) achieved CR after 2 and 4 cycles, respectively, whereas 6 (43%) obtained PR after received a median of 4 cycles (range; from 3 to 5 cycles). The duration of response were 20+ and 21+ months for CR, and the median 12 months ranging from 3 to 34 months for PR, respectively (Fig. 1).

Two patients discontinued cladribine after 2 cycles because of PD. One patient received salvage chemotherapy and radiotherapy, but died of disease progression in 14 months. Another patient was treated with 3 cycles of CHOP with rituximab, and achieved PR, and has survived in PR for 21 months.

Four patients fell into SD after 4 cycles of treatment. Two of them had disease progression in 3 and 10 months, respectively, while 2 other patients have been in SD for 18 and 25 months, respectively.

Table 1. Patient characteristics

UPN	Age/Sex	Histology	Stage at cladribine therapy	FLIPI at cladribine therapy	Prior therapy	Time to cladribine therapy from diagnosis (months)	Time to cladribine treatment from last therapy (months)	Response
1	63/F	Follicular lymphoma, grade 1	IIA	I	CHOP (PR), Radiation (PR), R-COP (PR)	96	30	PR
2	56/M	Follicular lymphoma, grade 1	IIA	L	R-CHOP (CR), COP (PR), VP-16 (SD)	33	7	SD
3	46/F	Follicular lymphoma, grade 2	IIIA	I	CHOP (CR), R-CHOP (CR)	96	50	CR
4	46/F	Follicular lymphoma, grade 2	IIIB	I	R-CHOP (PR)	14	13	PR
5	44/F	Follicular lymphoma, grade 1	IIA	L	CHOP (PR), R-COP (PR)	81	48	SD
6	65/F	Follicular lymphoma, grade 2	IVA	H	R-CHOP (PR), Radiation (PR)	36	26	PD
7	49/M	Follicular lymphoma, grade 2	IIA	L	CHOP (CR), R-CDE-11 (PR), Radiation (PR)	55	19	PR
8	66/F	Marginal zone B-cell lymphoma	IIA	L	CHOP (PR), R-CHOP (PR)	57	18	SD
9	68/F	Follicular lymphoma, grade 2	IIA	L	R-CHOP (PR)	23	23	PD
10	77/F	Follicular lymphoma, grade 2	IIIA	H	Rituximab (PR)	27	13	CR
11	63/M	Small lymphocytic lymphoma	IVA	H	CHOP (PR), R-CHOP (PR), COP (PR), CDE-11 (SD)	49	5	PR
12	44/M	Follicular lymphoma, grade 2	IIA	L	R-CHOP (PD)	3	3	SD
13	63/M	Follicular lymphoma, grade 2	IIIA	H	R-CHOP (PR)	18	17	PR
14	59/F	Follicular lymphoma, grade 2	IIIA	I	R-CHOP (CR)	65	64	PR

UPN, unique patient number ; FLIPI, Follicular Lymphoma International Prognostic Index ; L, low ; I, intermediate ; H, high ; CR, complete response ; PR, partial response ; SD, stable disease ; PD, progressive disease ; CHOP ; Cyclophosphamide + Doxorubicin + Vincristine + Prednisolone, R ; Rituximab, COP ; Cyclophosphamide + Vincristine + Prednisolone, VP-16 ; Etoposide, CDE-11 ; Carboplatin + Dexamethasone + Etoposide + Irinotecan

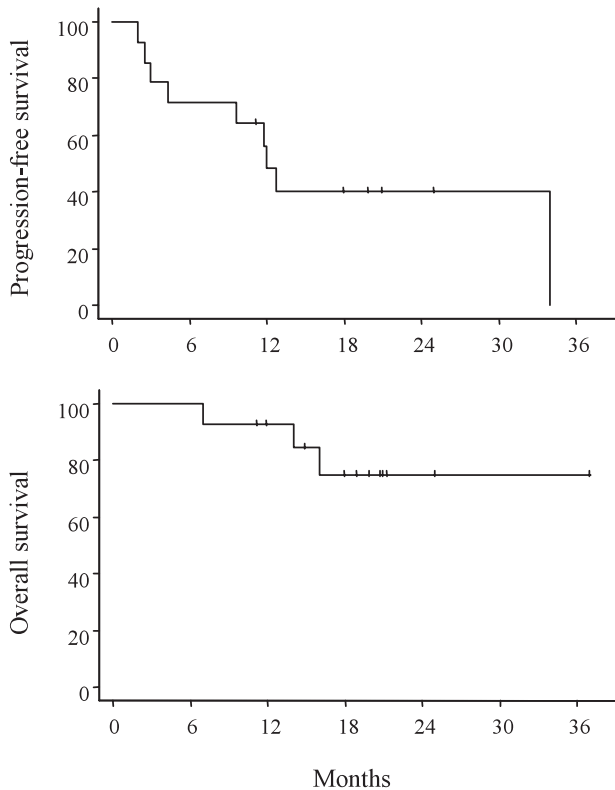


Fig. 1. The progression-free survival time and the overall survival time for all 14 patients enrolled in this study by Kaplan-Meier method.

To date, a total of 3 patients have died of disease progression. The median survival of all 14 patients from study entry was 18.5 months (range, from 7 to 37+) (Fig. 1).

Toxicity

Hematological toxicities are shown in Table 2. Neutropenia, anemia and thrombocytopenia were observed in 57%, 57% and 64% of patients, respectively. Grade 3 or 4 neutropenia occurred in 43% of patients, while neither anemia nor thrombocytopenia greater than grade 3 was observed. The most significant adverse event was lymphocytopenia. Lymphocyte counts decreased in all 14 patients, and grade 3 or 4 lymphocytopenia developed in 10 (71%). In these 10 patients, it took a median of 39 days (range ; 15 to 324) for lymphocyte counts to recover to $\geq 0.5 \times 10^9/L$ (\leq grade 2) after discontinuation of therapy. There was no febrile neutropenia or opportunistic infection during cladribine treatment.

Non-hematological toxicities were very mild, as shown in Table 3. One patient developed grade 3 hypoalbuminemia which was considered to be due to disease activity and reversed to normal levels during cladribine treatment. No other toxicity more than grade 3 was observed.

Two patients developed prolonged skin eruption with pruritus. A 44-year-old male suffered from generalized pruritus 1 month after the 4th cycle of cladribine therapy. He showed papules on his face, trunk, and extremities. The skin biopsy showed mild to moderate perivascular and interstitial inflam-

Table 2. Hematological toxicities

UPN	Grade of toxicities			
	Neutropenia	Lymphocytopenia	Anemia	Thrombocytopenia
1	4	3	1	1
2	0	2	1	0
3	3	3	0	1
4	4	4	1	1
5	0	2	0	0
6	0	3	0	0
7	3	4	1	1
8	3	3	0	1
9	0	3	0	0
10	0	3	2	2
11	3	2	1	0
12	2	1	1	2
13	0	3	0	2
14	2	4	1	1

UPN, unique patient number

Table 3. Non-hematological toxicities

UPN	Grade of toxicities											
	Fatigue	Constipation	Weight gain	Rash	Hypo -albuminemia	Hyper -bilirubinemia	Elevated AST	Elevated Cr	Hyponatremia	Hyperkalemia	Hypokalemia	
1	1	0	0	0	0	1	0	0	0	0	0	0
2	0	0	0	0	1	0	0	0	0	0	2	0
3	0	2	1	0	3	0	0	0	1	0	0	0
4	0	2	0	0	1	0	0	0	0	0	0	1
5	0	2	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	1	0	0	0	0	0	0	0
10	0	0	1	0	1	0	0	1	1	1	0	0
11	0	0	0	0	1	0	0	0	0	0	0	0
12	0	0	0	2	0	0	1	0	0	0	0	0
13	0	0	0	2	0	0	0	0	1	1	0	0
14	0	0	0	0	1	0	1	0	0	0	0	0

UPN, unique patient number ; AST, aspartate aminotransferase ; Cr, creatinine

matory infiltrates including lymphocytes and eosinophils in dermis. Dense neutrophilic infiltration in the follicle was also found. All drugs including cladribine and trimethoprim-sulfamethoxazole were discontinued, and antihistamine and corticosteroid were given. However, the skin lesions remained and he needed to receive antihistamine for more than 1 year. A 63-year-old man also developed papules with itching on his trunk 1 week after the first cycle of cladribine treatment. Trimethoprim-sulfamethoxazole compound was discontinued and antihistamine was given. He received another 3 cycles of cladribine with oral corticosteroid. The skin

lesions and itching continued during the treatment, and subsequently disappeared 6 months after the last cycle of therapy.

DISCUSSION

The pharmacokinetics of cladribine were previously investigated.⁴ Twelve patients were treated with 0.14 mg/kg of cladribine as a 2-hour infusion on days 1, 3, 4 and 5, and as a 24-hour continuous infusion during day 2. Blood samples were taken on days 1 and 2, and plasma concentrations were analyzed. The mean plasma cladribine concentrations of all

12 patients given by 2-hour infusion fitted well into a three-compartment model with the α -, β -, and γ -half-lives were 8 min, 1 hr and 6.3 hr, respectively. The AUC for the 2-hour and continuous infusion were 588 ± 185 and 552 ± 258 nM \times hour, respectively. The long γ -phase after the 2-hour infusion and the comparative AUC after 2-hour and continuous infusion suggest that cladribine can be administered intermittently with retained antitumor activity when compared to continuous infusion.

Cladribine was originally studied at a dose of 1.0 mg/kg/day by 24-hour continuous infusion for the treatment of low-grade lymphoma. The response was reported to be 43% including 20% CR and 23% PR, and the median response duration was 5 months.¹² For the Japanese phase II study, 0.09 mg/kg per day of cladribine was given by continuous intravenous infusion for 7 days. The response rate of CR and PR was 14% and 44.2%, respectively, and the median duration of CR and PR was 1183⁺ and 224 days, respectively.¹³ The results were comparable with those in the present study. We administered cladribine at a daily dose of 0.09 mg/kg by 2-hour intravenous infusion for 5 consecutive days in patients with relapsed or refractory indolent B-cell lymphoma. CR and PR were obtained in 14% and 43% of the patients, respectively, and the median duration of CR and PR was 20.5⁺ and 12 months, respectively. Similar results were reported by the European studies, in which cladribine at a dose of 0.12 mg/kg was given by 2-hour intravenous infusion for 5 days. The study resulted in achieving CR of 12.8-14% and PR of 28-38.3%, with the median duration for CR of 12-23 months and PR of 6-16 months, respectively.^{8,9} It indicates that the response rate and duration are similar in the relapsed or refractory indolent B-cell lymphoma treated with cladribine, regardless of infusion time.

Myelosuppression is the most common toxicity of cladribine. In the present study, the overall incidence of developing neutropenia, lymphocytopenia, anemia and thrombocytopenia were 57%, 100%, 57% and 64%, respectively. Grade 3 or 4 toxicity was observed in neutropenia (43%) and lymphocytopenia (71%), but not in anemia and thrombocytopenia. Robak *et al.* underwent 2-hour infusion of cladribine and showed that 19.2%, 6.4%, and 21.3% of patients had grade 3 or 4 neutropenia, anemia and thrombocytopenia, respectively.⁸ On the contrary, cladribine was given in continuous infusion in the Japanese phase II study. Neutropenia, anemia and thrombocytopenia developed in 77.8%, 42.2% and 55.6% of the patients, respectively, and those of grade 3 or 4 occurred in 53.3%, 17.8% and 37.8% of the patients, respectively.¹³ Lymphocyte counts decreased to less than 50% of the pretreatment levels in all patients and the median lymphocyte nadir was $0.2 \times 10^9/L$. It appears that overall hematological toxicities of cladribine given in 2-hour infusion were not worse than those administered in continuous infusion.

Two (14%) of 14 patients developed cutaneous reactions in our study. Cutaneous manifestations were also observed in 7 (21%) of 33 patients treated with continuous infusion of cladribine,¹⁴ indicating that this toxicity was not associated with the intermittent 2-hour infusion therapy. It seems that cladribine-induced skin lesions are long-lasting as compared with those experienced by other chemotherapeutic agents.¹⁵ It is of note that the interval between the start of cladribine and the first manifestation of cutaneous lesions are quite different from one patient to the other.¹⁴ In the present study, maculopapular exanthema developed during the first cycle of cladribine in one patient, while this was observed after the fourth cycle of cladribine in another patient, and the lesions lasted for 6 and 12⁺ months. It is considered that other drugs, such as trimethoprim-sulfamethoxazole and allopurinol, given simultaneously with cladribine, may have contributed to these skin lesions.^{16,17} Cladribine is shown to induce CD4⁺ lymphocytopenia and imbalance of T cell subsets,¹⁸ leading to an immunological dysregulation such as autoimmune hemolytic anemia. It is also suggested that the drug hypersensitivity may be caused by prolonged low levels of CD4⁺ lymphocytes,¹⁷ as observed in human immunodeficiency virus-infected patients. The drug hypersensitivity is not life-threatening but one of the annoying complications for patients treated with cladribine because persistent itching worsens their quality of life.

The combination chemotherapy of cladribine and other anti-lymphoma agents has been investigated in patients with low-grade B-cell lymphoma. A randomized comparison of cladribine alone and cladribine and cyclophosphamide combination therapy was studied in previously untreated patients.¹⁹ A higher probability of CR was obtained in the combination arm, although hematological toxicity was increased. Rummel *et al.* reported that cladribine and mitoxantrone combination was highly active against mantle-cell lymphoma and low-grade lymphoma resulting in a high overall response and a long remission duration.²⁰ However, Robak *et al.* showed that the addition of mitoxantrone and dexamethasone was not of advantage compared to cladribine alone in a phase II trials.²¹ There is no randomized trial comparing the efficacy of cladribine and mitoxantrone combination with that of cladribine alone. Retrospective analysis showed that when rituximab was given in addition to cladribine, the duration of response was improved.²² It is considered that combination with rituximab is a promising approach, since the addition of rituximab to another available antimetabolite, fludarabine, in combination with cyclophosphamide and mitoxantrone significantly increases the response rate and prolonged survival in a phase III trial.²³ The prospective trial would be required to investigate the efficacy and feasibility of cladribine-combination therapy in patients with low grade B-cell lymphoma.

In conclusion, we treated 14 patients of previously treated

indolent B-cell lymphoma with cladribine at a daily dose of 0.09 mg/kg by 2-hour intravenous infusion for 5 consecutive days at a schedule of every 4-weeks. The response rate and duration as well as the toxicity were similar to those of the same dose by continuous intravenous infusion for 7 days. It is concluded that cladribine can be administered by 2-hour infusion, while maintaining anti-lymphoma activity and acceptable toxicity profiles seen in continuous infusion. When one sees the patients who have to be admitted to the hospital and receive a cladribine injection through an indwelling intravenous catheter all day long by continuous infusion for 7 days, it is evident to everyone that 2-hour infusion for 5 days is more convenient and less expensive for the patients and their family. Further studies are warranted to confirm the tumor response and toxicities as well as quality of life of the patients who need years of treatment and follow up.

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