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Durable Response but Prolonged Cytopenia after Cladribine Treatment in Relapsed Patients with Indolent non-Hodgkin's Lymphomas: Results of a Japanese Phase II Study

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Abstract

We conducted a phase II study to evaluate the efficacy and safety of cladribine (2-chlorodeoxyadenosine [2-CdA]) for patients with refractory or relapsed indolent B-cell lymphoma or mycosis fungoides. Forty-five patients were enrolled, and 43 patients, including 34 with follicular lymphoma, were eligible. 2-CdA was given by continuous intravenous infusion at a dose of 0.09 mg/kg daily for 7 consecutive days, and this schedule was repeated every 4 weeks up to a maximum of 6 cycles. The overall and complete response rates were 58.1% (25/43; 90% confidence interval, 44.5%-70.9%) and 14.0% (6/43), respectively. The disease progression–free proportions of all 43 eligible and all 25 responding patients at 2 years were 30.3% and 48.1%, respectively. Neutropenia and thrombocytopenia of grade 3 or 4 were observed in 53.3% and 37.8% of patients, respectively, with prolonged cytopenia observed in patients with increased numbers of treatment cycles. Nonhematologic toxicities of grade 3 or greater included diarrhea, arrhythmia, malaise, and gastrointestinal bleeding in 1 patient each, an increase in glutamic-pyruvic transaminase level in 2 patients, and infection in 5 patients. Two treatment-related deaths were observed. Four patients developed myelodysplastic syndrome (MDS) at 13 months to 2 years after completion of the 2-CdA treatments. 2-CdA is an active agent with acceptable toxicity for refractory or relapsed indolent lymphoma; however, prolonged myelosuppression and the potential development of MDS should be carefully monitored.

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Key words: Cladribine; 2-CdA; Indolent lymphoma; Phase II study; Prolonged cytopenia; Secondary MDS

1. Introduction

Indolent non-Hodgkin's lymphomas (NHLs) are characterized by an advanced stage at presentation, lack of symptoms associated with the disease, and indolent behavior in terms of the time to symptomatic disease progression [1,2]. Despite good response rates, patients in advance stages are not curable with conventional chemotherapy regimens [3-7]. In addition, most patients inevitably relapse or progress, and no treatment strategy gives a durable response [8,9]. For these reasons, novel therapeutic agents and strategies need to be evaluated in this group of patients.

Cladribine (2-chlorodeoxyadenosine [2-CdA]) is a chlorinated purine analog that is resistant to degradation by adenosine deaminase and is toxic to lymphocytes in vitro

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[10]. The phosphorylated active form of 2-CdA accumulates in lymphocytes with high deoxycytidine kinase activity, resulting in DNA strand breaks and cell death. 2-CdA is cytotoxic to both resting and proliferating lymphocytes [11] and thus has potential efficacy in treating indolent lymphoid neoplasms, such as chronic lymphocytic leukemia (CLL) [12-15], hairy cell leukemia (HCL) [16,17], and indolent NHL [18-23]. Previously, we reported the results of our preceding phase I clinical trial of 2-CdA in which administration for 7 days at a dose of 0.09 mg/kg per day by continuous intravenous infusion generated objective responses in 3 of the 6 eligible patients [21]. This dose was recommended for the subsequent phase II study.

The primary purpose of this phase II study was to determine the efficacy and safety of 2-CdA administration at a dose of 0.09 mg/kg per day by 7-day continuous intravenous infusion in Japanese patients with refractory or relapsed indolent NHL.

2. Patients and Methods

2.1. Study Design

The present trial was a prospective, multi-institutional phase II study initiated in August 1996. The protocol was approved by the institutional review board of each participating institution. The study was performed in keeping with good clinical practice regulations. The study was closed for accrual in January 1999.

2.2. Patients

Previously treated patients with indolent lymphoid neoplasms were eligible if they met the following criteria: (1) histologic and/or cytologic confirmation of indolent NHL categorized as peripheral B-cell neoplasms numbered 1 to 5 or as mycosis fungoides by a revised European-American classification of lymphoid neoplasms (REAL classification) [22]; (2) patients with lymphoma refractory to conventional chemotherapy, with relapse after attaining a complete response (CR), or with disease progression after attaining a partial response (PR); (3) no chemotherapy or irradiation within 2 weeks prior to the study; (4) life expectancy of at least 8 weeks; (5) age ≥15 years and <75 years; (6) performance status of 2 or better on the Eastern Cooperative Oncology Group scale; (7) adequate bone marrow function (neutrophil count ≥1200/μL, platelet count ≥100,000/μL, hemoglobin ≥8.0 g/dL), adequate hepatic function (bilirubin level <2.0 times the upper limit of normal, transaminase levels <2.5 times the upper limits of normal), adequate renal function (creatinine level <1.5 times the upper limit of normal), adequate pulmonary function (PaO_2 ≥65 mm Hg), and a normal electrocardiogram; (8) no severe complications; and (9) written informed consent.

2.3. Central Pathologic Review

Thin-layer slide preparations of lymphoma tissues obtained at the initial diagnosis and/or at the relapse were collected. These specimens were stained with hematoxylin-eosin. In addition, immunohistochemical analyses were conducted with antibodies, including an anti-CD20 monoclonal antibody (L26) [23], an anti-CD3 polyclonal antibody, and an anti–cyclin D1 monoclonal antibody [24,25]. Preparations stained with hematoxylin-eosin and immunohistochemically were microscopically examined by a central pathologic review committee composed of the following 3 hematopathologists: Drs. Y. Matsuno, S. Nakamura, and S. Mori. The diagnosis by the central pathologic review committee was regarded as the final one in cases in which there was discrepancy between the diagnosis of an institution and that of the committee.

2.4. Drug Formulation and Treatment

2-CdA was supplied by Janssen Pharmaceutical (Tokyo, Japan) as a 0.1% (1 mg/mL) solution of endotoxin-free 2-CdA in sterile 0.9% sodium chloride. The desired dosage of 2-CdA was added to normal saline in a total volume of 500 to 1000 mL, which was infused through a central or peripheral venous access. We administered 2-CdA at a dose of 0.09 mg/kg per day by continuous intravenous infusion for 7 days up to a maximum of 6 cycles. This schedule was based on the results of our preceding phase I study [21]. First, treatment was repeated every 28 days for 3 cycles unless patients developed progressive disease (PD) or severe adverse events, such as grade 4 hematologic toxicity and grade 3 or 4 nonhematologic toxicity. After 3 cycles of 2-CdA, all eligible patients were evaluated for therapeutic responses. Patients who achieved CR or PR and patients who expected to achieve further tumor regression by additional administrations of 2-CdA were able to receive up to a maximum of 6 cycles. The administration of 2-CdA was terminated immediately whenever PD was confirmed. The use of other anticancer agents and radiotherapies was prohibited during the study period.

2.5. Supportive Care

Prophylaxis of *Pneumocystis carinii* infection and tuberculosis (only in high-risk patients) was achieved with orally administered trimethoprim-sulfamethoxazole and isoniazid, respectively. Broad-spectrum antibiotics were used for suspected bacterial infections. Administration of granulocyte colony-stimulating factor was planned when grade 3 or greater neutropenia and leukopenia developed. Acyclovir and ganciclovir were not recommended for prophylactic use but were used for the treatment of herpes virus infection and cytomegalovirus infection, respectively.

2.6. Response and Toxicity Criteria

Tumor response was assessed according to World Health Organization criteria [26]. The response was evaluated by computed tomography scanning, by direct measurement of superficial lymph nodes, and, if necessary, by bone marrow aspiration. CR was defined as the disappearance of all clinical evidence of disease and the normaliza-

tion of all laboratory values and radiographic results lasting for at least 4 weeks. PR was defined as a reduction of 50% or more in the sum of the products of the cross-sectional diameters of all known lesions lasting for at least 4 weeks. PD was defined as the occurrence of new lesions or as an increase of 25% or more in the sum of the products of the cross-sectional diameters of all previously detected lesions. All other categories of tumor response were defined as no change.

Hematologic and nonhematologic toxicities were evaluated in all treated patients according to the toxicity-grading criteria of the Japan Clinical Oncology Group [27], which is an expanded version of National Cancer Institute Common Toxicity Criteria version 1.0. Blood cell counts were examined twice a week, and clinical observations and other routine laboratory tests were performed weekly.

2.7. Statistical Analysis and Sample Size

The primary end point was the overall response rate (ORR) in eligible patients. Analysis of the ORR was carried out by means of point estimates and the 90% confidence interval (CI). This study adopted a 2-stage design including an interim analysis. Assuming that the expected and threshold ORRs are 40% and 20%, respectively, at α = 5% (1-tailed) and β = 20%, we calculated the minimal sample size by Simon's minimax method to be 33 patients. To take into account the possible inclusion of ineligible patients who might be detected later by the central pathologic review, we set the target number of patients at 50. If the upper limit of the 90% CI of the ORR in the planned interim analysis did not reach 40%, the study would be discontinued. Progression-free survival (PFS) was defined as the time between the start of 2-CdA treatment and progression, relapse, initiation of alternative therapy, or death from any cause, whichever occurred first. The duration of response was defined as the number of days from the first day of achieving CR or PR until the day when relapse or progression was diagnosed or until the final day of observation. The minimum and maximum values for the PFS and the duration of response were determined, and the Kaplan-Meier method was employed to estimate the 50% point and its 90% CI [28]. The analytical software used was SAS version 6.12 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Patient Accrual and Interim Analysis

Forty-five patients with relapsed or refractory NHL were enrolled between August 1996 and January 1999. The patient characteristics are shown in Table 1.

Agreement between the diagnosis by each institution (site diagnosis) and that by the central pathologic review committee (consensus diagnosis) was 97.8% (44/45). The central pathologic review determined that 35 patients had follicular lymphoma, 4 had mantle cell lymphoma, 3 had marginal zone B-cell lymphoma, and 2 had mycosis fungoides. Two patients were judged ineligible by the extramural review committee after they had received 2-CdA. In 1 patient, the histologic diagnosis was corrected from follicular large cell lymphoma to diffuse large B-cell lymphoma by the central pathologic review committee, and in the other patient previous chemotherapy had been given within 2 weeks before 2-CdA treatment. All 45 patients treated were evaluated for toxicity. Therapeutic efficacy was evaluated in the 43 eligible patients and in all 45 patients enrolled. The median age was 50 years (range, 26-73 years), and the male-female ratio was 27:16.

Table 1.
Demographic and Other Baseline Characteristics*

	Enrolled Patients (n = 45)	Eligible Patients (n = 43)
Sex, n		
Male	29	27
Female	16	16
Age, y†	49 (26-73)	50 (26-73)
Weight, kg†	59.6 (42.8-81)	58.7 (42.8-81)
Pathology		
B-cell neoplasms, n		
Follicle center lymphoma, follicular	35	34
Mantle cell lymphoma	4	4
Marginal zone B-cell lymphoma	3	3
Diffuse large B-cell lymphoma	1	0
T-cell neoplasms, n		
Mycosis fungoides	2	2
Disease status, n		
Primary refractory	7	7
Relapsed	22	21
Refractory after relapse	16	15
Performance status, n		
0	30	29
1	13	12
2	2	2
Clinical stage, n		
I	2	2
II	7	7
III	12	12
IV	24	22
Time to 2-CdA treatment initiation from diagnosis, n		
<1 y	6	6
≥1 y, <5 y	27	26
≥5 y, <10 y	10	9
≥10 y, <15 y	2	2
Prior therapy		
Chemotherapy, n		
None	0	0
Done	45	43
Radiotherapy, n		
None	34	32
Done	11	11
Auto-PBSCT, n		
None	40	39
Done	5	4
Rituximab, n		
None	35	34
Done	10	9
No. of regimens†	2 (1-14)	2 (1-14)

*2-CdA indicates cladribine; Auto-PBSCT, autologous peripheral blood stem cell transplantation.

†Data are presented as the median (range).

Table 2.
Responses by Histologic Subtype*

	CR, n	PR, n	NC, n	PD, n	ORR	90% CI	%CR	90% CI
All eligible patients (n = 43)	6	19	9	9	58.1%	44.5%-70.9%	14.0%	6.3%-25.7%
Histologic subtype								
FL (n = 34)	5	14	7	8	55.9%		14.7%	
MCL (n = 4)	0	2	1	1	50.0%		0%	
MZL (n = 3)	1	2	0	0	100%		33.3%	
MF (n = 2)	0	1	1	0	50.0%		0%	

*CR indicates complete response; PR, partial response; NC, no change; PD, progressive disease; ORR, overall response rate; CI, confidence interval; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone B-cell lymphoma; MF, mycosis fungoides.

The number of prior chemotherapeutic regimens was 1 in 11 patients and 2 or more in the remaining 32 patients (74.4%). Stage III and IV disease was present in 12 patients (27.9%) and 22 patients (51.2%), respectively (Table 1). The numbers of patients who were primary refractory, relapsed, and refractory to the preceding chemotherapy regimens were 7 (16.3%), 21 (48.8%), and 15 (34.9%), respectively.

3.2. Responses

Of 20 eligible patients in the interim analysis, 1 achieved CR, and 11 achieved PR (ORR, 60.0%; 90% CI, 39.4%-78.3%). Because the upper limit of the 90% CI of the ORR reached 40.0%, we continued patient enrollment. As shown in Table 2, 25 of 43 eligible patients achieved objective responses (ORR, 58.1%; 90% CI, 44.5%-70.9%). Among the 25 responders, 6 achieved CR (13.9%; 90% CI, 6.3%-25.7%). The main characteristics of all 25 responders are presented in Table 3. When we analyzed the responses according to histologic subtype, no difference was observed between follicular lymphoma and other types of indolent NHLs. CR was achieved in 5 (14.7%) of 34 patients with follicular lymphoma and in 1 of 3 patients with marginal zone lymphoma (Table 2). The median times to achieve a response and CR were 36 days (range, 16-163 days) and 88.5 days (range, 25-475 days), respectively, and the onset of induction of a response occurred within 2 cycles in most of the responders (76.0%, 19/25). Twenty-two patients (51.2%) received 3 or more cycles of 2-CdA, and the remaining 21 received only 1 or 2 cycles only because of PD, toxicity, or refusal. The numbers of patients who showed PD after the first and second cycles were 6 and 4, respectively. The numbers of patients who received 4, 5, or 6 cycles of 2-CdA were 8, 4, and 1, respectively.

The patients who had responded to prior chemotherapy regimens responded more frequently to 2-CdA treatment than those who had been refractory to prior chemotherapies (17/23 [73.9%] versus 8/20 [40.0%]; $P = .0333$). No association was observed between the response and a history of treatment with irradiation, high-dose chemotherapy with hematopoietic stem cell transplantation, or rituximab. Regarding the efficacy of 2-CdA in 9 patients previously treated with rituximab monotherapy, 2 of 6 patients who were refractory to prior rituximab therapy and 2 of 3 patients who had relapsed after PR induced by rituximab therapy achieved PR in response to 2-CdA treatment.

At a median follow-up period of 302 days (range, 70-1924+ days) in the 25 responders, the following events indicating treatment failure were observed: progression after PR in 15 patients and relapse after CR in 2 patients. The estimated median PFS times for all 43 eligible patients and all 25 responding patients were 239 days (90% CI, 104-302 days) and 386 days (90% CI, 276-1234 days), respectively (Figures 1 and 2). The progression-free proportions of all 43 eligible patients and all 25 responding patients were 33.4% and 53.0%, respectively, at 1 year and 30.3% and 48.1% at 2 years.

The median duration of response in the 25 responders was estimated to be 282 days (90% CI, 224-694 days). The median duration of CR was 1183+ days (range, 282-1450+ days), whereas the median duration of PR was 224 days (range, 30-1333 days) (Table 3).

3.3. Toxicities

All 45 treated patients were evaluable for toxicity. The main toxicities of 2-CdA were hematologic toxicities, especially neutropenia and thrombocytopenia. The times to the nadir of the neutrophil count were mostly between 2 weeks and 3 weeks, whereas those for platelets were more than 4 weeks after treatment initiation. The times to recovery from the nadir of the neutrophil count were 1 or 2 weeks. In contrast, only a few patients showed recovery of the platelet count during the washout period until the initiation of the subsequent cycle, and the recovery and alleviation rates decreased as the number of cycles increased. Neutropenia and thrombocytopenia of grade 3 or 4 were observed in 53.3% and 37.8% of patients, respectively (Table 4). Among these patients, long-term neutropenia and thrombocytopenia lasting for more than 100 days were observed in 8 patients each. Neutropenia and thrombocytopenia did not recover from their nadirs by the last observation in 3 patients and 5 patients, respectively.

As was also expected, 2-CdA induced considerable lymphocytopenia. A lymphocyte nadir of less than 50% of the pretreatment value was observed in 100% of 44 patients. The median peripheral lymphocyte count before treatment was 1115/μL (baseline level), and 1 week after initiation of 2-CdA treatment it reached 204/μL ($P < .0001$). The time for recovery of the lymphocyte count to the baseline level after the completion of treatment was 12 months or longer. A $CD4^+$ lymphocyte count nadir of less than 50% of the pretreatment value was observed in 63.3% of 30 evaluable patients. Whereas the median CD4/CD8 ratio was 1.05 before treatment with 2-CdA, the ratios after the first, second, and third cycles were 0.96 ($P = .4217$), 0.39 ($P = .0002$),

Table 3.
Characteristics of 25 Responders*

Diagnosis (Immunophenotype)	Clinical Stage	Prior Therapy (Response)†	Disease Status	Cladribine Treatment Cycles, n	Response	Duration of Response, d
FL (B)	I	CHOP (PR); [1]	Relapsed	3	PR	114
FL (B)	II	CHOP (CR); [1]	Relapsed	5	CR	282
FL (B)	III	CHOP (CR); [1]	Relapsed	4	CR	1416+
FL (B)	III	CHOP (NC); DeVIC (NC); C-MOPP (CR); [3]	Relapsed	3	CR	371
FL (B)	III	CHOP (CR); Rad (CR); [1]	Relapsed	4	PR	694
FL (B)	III	LSG-9 (CR); VP-16 (NC); [2]	Relapsed	3	PR	1202
FL (B)	III	Epi + CPA + VCR + PDN (PR); Epi + CPA + VCR + PDN (CR); Rad (PR); [1]	Relapsed	3	PR	595
FL (B)	III	CHOP (PR); VENP (VCR→VDS) (NC); [2]	Primary refractory	4	PR	75+
FL (B)	IV	CHOP (PR); [1]	Primary refractory	3	CR	1273+
FL (B)	IV	Biweekly CHOP (PR); CPA + PSL (NC); [2]	Primary refractory	3	CR	1230
FL (B)	IV	CHOP (NC); [1]	Primary refractory	6	PR	1333
FL (B)	IV	LSG-9 (CR); THP–LSG-9 (PR); [2]	Relapsed	4	PR	703
FL (B)	IV	VCR + CPA + ADM + PDN (CR); VDS + VP-16 + PCZ + PDN (CR); C-MOPP (CR); VDS + CPA + PDN (PD); MIT + VP-16 + VDS + PDN (PR); CPA + VP-16 + ABMT (CR); rituximab (PD); [7]	Relapsed	3	PR	276
FL (B)	IV	LSG-4 (CR); MX2 + ACNU + THP + VDS + PSL (NC); VIPP (PR); VENP (NC); CBDCA + IFM + VP-16 (PR);VP-16 (PD); MIT + Ara-C + CEM (CR); SBZ + VP-16 (NC); HD-MTX (PR); rituximab (PR); Rad (CR); Rad (PD); Rad (PR); [10]	Refractory after relapse	2	PR	236
FL (B)	IV	CHOP (PR); VP-16 (NC); C-MOPP (NC); rituximab (PR) ×2; [4]	Relapsed	3	PR	224
FL (B)	IV	LSG-4 (CR); THP-VEPA (CR); Chemo + PBSCT (CR); modified EPOCH (PR); [4]	Relapsed	3	PR	163
FL (B)	IV	VCP (CR) ×4; AVCP (CR); C-MOPP (CR); rituximab (NC); [4]	Relapsed	3	PR	71
FL (B)	IV	CHOP (PR); MACOP-B (NE); Rad (PR); [2]	Relapsed	2	PR	56
FL (B)	IV	CHOP (PR); CAMVD (PR); PCZ (PR); VDS + MTX (PR); Rad (CR); [4]	Relapsed	2	PR	30
MCL (B)	IV	VCR + CPA + PSL (PR); Rad (PR); [1]	Relapsed	3	PR	1280
MCL (B)	IV	VEPA (PR); COP (PD); [2]	Refractory after relapse	5	PR	169
MZL (B)	II	VEPA (CR); VEMP (CR); [2]	Relapsed	2	CR	1900+
MZL (B)	III	VEPA (PR); COP (NC); Ope (CR); [2]	Refractory after relapse	2	PR	249
DL (B); transformed from MZL	I	CHOP (CR); TUT-7 (NC); VP-16 (NC); VENP (CR); VENP (PR); Rad (CR); [4]	Refractory after relapse	1	PR	143
MF (T)	IV	MACCEPOMB (PR); CPT-11 (NC); [2]	Refractory after relapse	5	PR	66

*FL indicates follicle center lymphoma, follicular; CHOP, regimen of cyclophosphamide (CPA) + doxorubicin (ADM) + vincristine (VCR) + prednisolone (PSL); PR, partial response; CR, complete response; NC, no change; DeVIC, regimen of dexamethasone (Dex) + etoposide (VP-16) + ifosfamide (IFM) + carboplatin (CBDCA); C-MOPP, regimen of CPA + VCR + procarbazine (PCZ) + PSL; Rad, radiation; LSG-9, third-generation combination chemotherapy consisting of VCR, CPA, ADM, bleomycin (BLM), PSL, methotrexate (MTX), vindesine (VDS), VP-16, and PCZ; Epi, epirubicin; PDN, prednisone; VENP, regimen of VCR + CPA + PCZ + PSL; THP, tetrahydropyranyl ADM; PD, progressive disease; ABMT, autologous bone marrow transplantation; LSG-4, second-generation combination chemotherapy consisting of the same 9 agents as LSG-9; MX2, 3′-deamino-3′-morpholino-13-deoxo-10-hydroxycarminomycin; ACNU, nimustine hydrochloride; VIPP, regimen of VCR + IFM + PCZ + PSL; MIT, mitoxantrone; Ara-C, cytosine arabinoside; CEM, regimen of CPA + VP-16 + melphalan; SBZ, sobuzoxane; HD-MTX, high-dose MTX; VEPA, regimen of VCR + CPA + PSL + ADM; Chemo, chemotherapy; PBSCT, peripheral blood stem cell transplantation; EPOCH, regimen of VP-16 + PSL + VCR + CPA + ADM; VCP, regimen of VCR + CPA + PSL; AVCP, regimen of ADM + VCR + CPA + PSL; MACOP-B, regimen of MTX + ADM + CPA + VCR + PSL + BLM; CAMVD, regimen of CBDCA + MIT + VCR + Dex; MCL, mantle cell lymphoma; COP, regimen of CPA + VCR + PSL; MZL, marginal zone B-cell lymphoma; VEMP, regimen of VCR + CPA + MTX + PSL; Ope, operation; DL, diffuse large B-cell lymphoma; TUT-7, menogaril; MF, mycosis fungoides; MACCEPOMB, regimen of MTX + ADM + CPA + CBDCA + VP-16 + PSL + VCR + MIT + BLM; CPT-11, irinotecan.

†Numbers in brackets indicate number of prior chemotherapeutic regimens.

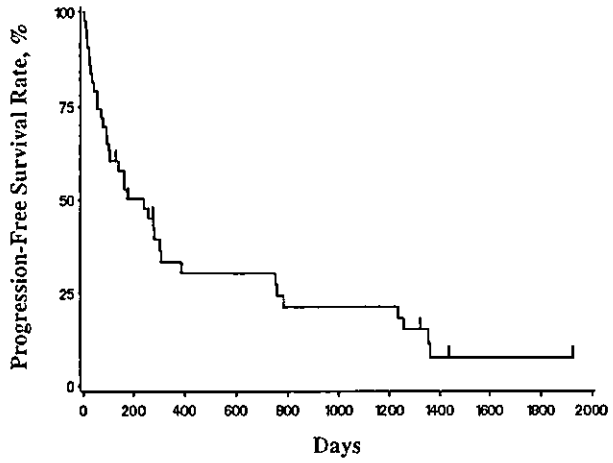

Figure 1. The progression-free survival time for all 43 eligible patients at the 50% point was estimated by the Kaplan-Meier method to be 239 days (90% confidence interval, 104-302 days).

and 0.31 ($P < .0001$), respectively. The median $CD20^+$ B-cell count in the peripheral blood before treatment and the counts after the first, second, and third cycles were 86/μL, 9/μL ($P < .0001$), 18/μL ($P < .0001$), and 31/μL ($P = .0003$), respectively. A grade 3 decrease in the hemoglobin level was observed in 17.8% of all patients.

The most important nonhematologic toxicity was infection (Table 5). Infection was severe in some patients, including 2 deaths (1 case of interstitial pneumonia and 1 of generalized herpes simplex virus [HSV]infection) and 3 other grade 3 or 4 infectious episodes (1 case of grade 4 varicella-zoster virus, 1 of grade 3 hemorrhagic cystitis with pyelonephritis, and 1 of grade 3 fever of unknown origin). A 68-year-old male patient with grade II follicular lymphoma died from severe interstitial pneumonia during delayed and prolonged pancytopenia after the completion of 5 cycles of

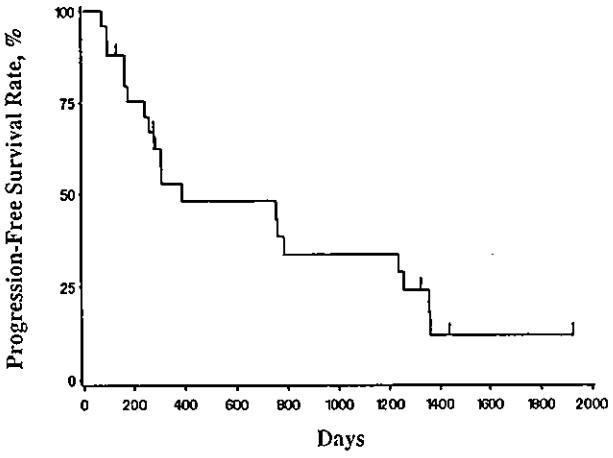

Figure 2. The progression-free survival time for all 25 responding patients at the 50% point was estimated by the Kaplan-Meier method to be 386 days (90% confidence interval, 276-1234 days).

2-CdA therapy. In addition, a 32-year-old man with grade III follicular lymphoma died from massive gastrointestinal bleeding complicated by a generalized HSV infection during combination chemotherapy (CHOP therapy [regimen of cyclophosphamide, doxorubicin, vincristine, and prednisolone]) that was initiated from 4 days after 1 cycle of 2-CdA because of rapid progression of the lymphoma. Including these 5 patients, 16 patients in total experienced infection. HSV and varicella-zoster virus infections were observed in 5 patients each. Other infections are listed in Table 5. All these infections fully resolved in response to appropriate treatment except for the 2 patients who died. Other grade 3 or 4 nonhematologic toxicities were grade 3 serum glutamic-pyruvic transaminase elevation in 2 patients, grade 3 diarrhea in 1 patient, grade 3 arrhythmia in 1 patient, and grade 4 malaise in 1 patient (the patient who died of interstitial pneumonia). Nonhematologic toxicities other than infection were rare and mild. No patients developed neurologic symptoms or alopecia.

3.4. Secondary Malignancies

A secondary malignancy observed throughout the present study was myelodysplastic syndrome (MDS) in 4 patients. In 3 patients, MDS with refractory anemia (MDS-RA) was confirmed at 20 months, 2 years, and 2 years after 2-CdA treatment. In addition, MDS was suspected in 1 patient 13 months after 2-CdA treatment. Three patients who developed MDS-RA died during the follow-up period. The contents and durations of prior treatment, 2-CdA treatment, and post–2-CdA treatment are listed in Table 6. All of these patients had received combination chemotherapies including alkylators, anthracyclines, and epipodophyllotoxins as prior therapy. Three of these patients had also received radiotherapy before and/or after 2-CdA treatment. Cytogenetic analysis detected abnormal karyotypes in all 4 patients. One patient who had received alkylating agents in the previous chemotherapies had an abnormal karyotype of +1,der(1;7); another patient had –Y. The other 2 patients who had received both topoisomerase II inhibitors and alkylating agents in the previous chemotherapies had abnormal karyotypes of –6,–7 and t(5;8)(q13,q24).

4. Discussion

The primary purpose of this multi-institutional phase II study was to evaluate the efficacy and the toxicity of 2-CdA with a schedule of continuous intravenous infusion at a dose of 0.09 mg/kg daily for 7 consecutive days in Japanese patients with refractory or relapsed indolent NHL. 2-CdA with this dose and schedule was effective for patients with relapsed or refractory indolent NHL. The ORR in 43 eligible patients was 58.1%, with 14.0% achieving CR. The results of several clinical trials have suggested that 2-CdA can induce objective responses in 43% to 55% of patients with relapsed or refractory indolent NHL [18,19,29-31]. The results of our present study demonstrated an efficacy that was similar to the efficacy data from these studies from Western countries.

The ORR for follicular lymphoma was 55.9% (90% CI, 40.5%-70.5%) in the present study. Kay et al reported a 50%

Table 4.
Adverse Drug Reactions*

	Patients, n	JCOG Toxicity Grade, n				Patients with ADR, n (%)	Patients ≥Grade 3, n (%)
		≤2	3	4	5		
Hematologic toxicity							
Leukopenia	45	9	22	5		36 (80.0)	27 (60.0)
Neutropenia	45	11	12	12		35 (77.8)	24 (53.3)
Thrombocytopenia	45	8	11	6		25 (55.6)	17 (37.8)
Hemoglobin decrease	45	11	8			19 (42.2)	8 (17.8)
Nonhematologic toxicity							
GPT elevation	44	9	2			11 (25.0)	2 (4.5)
Malaise	45	4		1		5 (11.1)	1 (2.2)
Diarrhea	45	2	1			3 (6.7)	1 (2.2)
Hemorrhage of gastrointestinal tract	45				1	1 (2.2)	1 (2.2)
Arrhythmia	35		1			1 (2.9)	1 (2.9)

*JCOG indicates Japan Clinical Oncology Group; ADR, adverse drug reaction; GPT; glutamic-pyruvic transaminase.

ORR in patients with refractory or relapsed follicular lymphoma treated with 2-CdA monotherapy [18]. Importantly, 6 of the 25 responders achieved CR, and 3 of these patients have been maintaining CR with a median follow-up duration of 1361+ days (range, 1210+-1450+ days). This observation is uncommon for a single agent in pretreated patients. A response was obtained in all 3 patients with marginal zone lymphoma, including 1 patient with transformed diffuse large B-cell lymphoma, and CR was obtained in 1 of these patients. Recently, 2-CdA was reported to be highly effective in inducing CR in 84% of chemotherapy-naive patients with lymphoma of mucosa-associated lymphoid tissue [32]. In the present study, 2 of 4 patients with mantle cell lymphoma and 1 of 2 patients with mycosis fungoides responded to 2-CdA. Mantle cell lymphoma is the most frequently incurable lymphoma [33]. Rummel et al reported that the combination of reduced-dose 2-CdA and mitoxantrone is a highly active regimen in the treatment of indolent lymphomas, especially mantle cell lymphoma [34]. The activity of 2-CdA in treating cutaneous T-cell lymphoma was evaluated in 16 patients who had relapsed after topical therapies only (7 patients) or after topical and systemic therapies (9 patients) [35]. In these investigators' series, 3 of 9 patients with mycosis fungoides responded, and 4 of 7 patients with non–mycosis fungoides histologic characteristics responded. Recently, an anti-CD20 monoclonal antibody (rituximab) has become widely used, with notable efficacy observed for B-cell indolent lymphoma. That 4 of 9 patients refractory or relapsed after rituximab monotherapy achieved PR with 2-CdA in the present study is highly noteworthy.

The most significant toxicity of 2-CdA is myelosuppression, which occurs at an acceptable incidence at the dose levels used in this and other phase II trials for the treatment of lymphoid malignancies. Neutropenia and thrombocytopenia of grade 3 or 4 were observed in 53.3% and 37.8% of patients, respectively. However, long-term neutropenia and thrombocytopenia lasting more than 100 days were observed in some patients who were pretreated extensively or had received more than 4 cycles of 2-CdA therapy. More than 4 cycles of 2-CdA with the dose and schedule used in the present study are not recommended for patients who have been heavily pretreated. Another notable hematologic toxicity was lymphocytopenia including $CD4^+$ T-cells and $CD20^+$ B-cells. Recovery from this lymphocytopenia to the baseline level took 12 months or

Table 5.
Infections*

Adverse Event	Patients, n	JCOG Toxicity Grade, n					Patients with AE, n (%)	Patients ≥Grade 3, n (%)
		1	2	3	4	5		
Total	45	5	6	2	1	2	16 (35.6)	5 (11.1)
Herpes simplex	45	2	2			1	5 (11.1)	1 (2.2)
Varicella-zoster	45	2	2		1		5 (11.1)	1 (2.2)
Sepsis	45		3				3 (6.7)	
Urinary tract infection	45	2					2 (4.4)	
Pneumonia, interstitial	45					1	1 (2.2)	1 (2.2)
Fever of unknown origin	45			1			1 (2.2)	1 (2.2)
Cystitis, hemorrhagic	45			1			1 (2.2)	1 (2.2)
Pyelitis	45			1			1 (2.2)	1 (2.2)
Cystitis	45		1				1 (2.2)	
Pharyngitis	45		1				1 (2.2)	
Forehead headache	45		1				1 (2.2)	
Cytomegalovirus infection	45	1					1 (2.2)	
Rash, bullous	45	1					1 (2.2)	

*JCOG indicates Japan Clinical Oncology Group; AE, adverse event.

Table 6.
Secondary Malignancies*

Case No.	Pathology (REAL classification)	Age, y/Sex	Prior Therapies (Response)	2-CdA Treatment Period	Post-2-CdA Therapies	Secondary Malignancy, Abnormal Karyotypes	Time to Onset from 2-CdA Completion
1	Mycosis fungoides	41/F	MACCEPOMB, 12/27/95–03/13/96 (PR); CPT-11, 11/11/96–12/16/96 (NC)	01/09/97–01/15/97, 02/06/97–02/12/97, 03/11/97–03/17/97, 04/08/97–04/14/97, 05/06/97–05/11/97 (5 cycles). Response, PR	Rad (50 Gy) intermittently for approximately 1 y from 06/18/97	MDS-RA, –6,–7	2 y
2	Mantle cell lymphoma	71/M	VCR + CPA + PSL, 12/16/94–02/08/95 (PR); Rad (50 Gy), 12/20/94–01/30/95 (PR)	05/23/97–05/29/97, 06/20/97–06/26/97, 07/18/97–07/24/97 (3 cycles). Response, PR	None	MDS-RA, +1,der(1;7)	2 y
3	Follicular lymphoma grade III	33/M	LSG-4, 03/88–03/89 (CR); MX2 + ACNU + THP + VDS + PSL, 08/90–01/91 (NC); VIPP, 01/91–03/92 (PR); VENP, 03/92–01/93 (NC); CBDCA + IFM + VP-16, 01/93–04/93 (PR); VP-16, 04/93–03/94 (PD); MIT + Ara-C + CEM, 03/94–08/94 (CR); SBZ + VP-16, 03/95–04/96 (NC); Rad (40 Gy), 04/13/95–05/16/95 (CR); Rad (40 Gy), 04/16/96–05/17/96 (PD); rituximab, 06/05/96–09/16/97 (PR); Rad (19.5 Gy), 06/24/98–07/14/98 (PR); HD-MTX, 07/21/98–09/07/98 (PR)	10/16/98–10/22/98, 11/17/98–11/23/98 (2 cycles). Response, PR	Rad (18-52.5 Gy) intermittently 06/29/99–07/14/00	MDS-RA, t(5;8)(q13,q24)	20 mo
4	Follicular lymphoma grade II	49/M	CHOP, 10/25/97–05/13/98 (PR)	12/02/98–12/08/98, 01/05/99–01/11/99, 02/01/99–02/07/99 (3 cycles). Response, PR	None	MDS suspected, –Y	13 mo

*REAL Classification indicates revised European-American classification of lymphoid neoplasms; 2-CdA, cladribine; MDS-RA, myelodysplastic syndrome with refractory anemia. All other abbreviations are expanded in the first footnote to Table 3.

longer from the time of completion of 2-CdA administration. In the present study, 2 patients died of severe infections (interstitial pneumonia and generalized HSV infection). HSV or varicella-zoster virus infection was observed in 10 patients. Grade 4 varicella-zoster virus infection was observed in 1 patient during careful follow-up for almost 2 years after 2-CdA therapy, and this infection was likely associated with immunosuppression mediated by 2-CdA. Therefore, adequate caution should be exercised regarding the prolonged immunosuppression mediated by 2-CdA. Thus, regular and frequent monitoring of peripheral blood counts and differentials of white blood cell counts should be done so that 2-CdA is administered safely. It is advisable to use drugs such as oral trimethoprim-sulfamethoxazole and acyclovir for prophylaxis of *Pneumocystis carinii* pneumonia and herpes viral infections, respectively.

In this study, MDS was found in 4 of 45 patients treated with 2-CdA. MDS was confirmed at 20 months, 2 years, and 2 years after completion of 2-CdA treatment in 3 patients and was suspected at 13 months after completion of treatment in the fourth patient. Because purine analogs such as 2-CdA, fludarabine, and 2'-deoxycoformycin induce moderate myelosuppression and profound and prolonged immunosuppression, there has been concern about the potential for an increased risk of a secondary malignancy in a group of patients whose disease already places them at a greater risk for second cancers [36-38]. However, Cheson et al reported favorable results in a study that assessed the frequency of secondary malignancies in patients with CLL who were treated with fludarabine (n = 724) and in patients with HCL who were treated with 2'-deoxycoformycin (n = 409) and with 2-CdA (n = 979) [39]. The conclusion was that despite patients' immunosuppression, nucleoside analogs could be safely administered to patients with CLL or HCL without a significantly increased risk of secondary malignancies. However, these investigators' conclusion obtained in an HCL series is impossible to extrapolate directly to patients with indolent NHL because there are 2 important points of difference. The first difference is that usually only 1 treatment cycle of 2-CdA is required to obtain the optimal response in HCL patients but multiple courses are needed in indolent NHL patients. The second difference is that the patients with HCL were mostly previously untreated, in contrast to the indolent NHL patients, who had been previously treated at the time of 2-CdA treatment. The total amount of 2-CdA administered is higher and the duration of exposure is longer in the treatment of indolent NHL than in the treatment of HCL. However, in the case of indolent NHL, it is difficult to exclude the risk of secondary malignancy due to treatments preceding 2-CdA treatment. Therapy-related MDS is being reported with increasing frequency as a recognized complication of conventional chemotherapy for lymphomas [40]. It was first recognized among adults treated with alkylators, but other drugs, including epipodophyllotoxins and anthracyclines, as well as procedures such as radiotherapy and autologous bone marrow transplantation have now been implicated in the development of secondary malignancies [40-45]. In addition, the frequency of therapy-related MDS was reported to rise in patients treated with both radiotherapy and chemotherapy, compared with patients treated with radiotherapy alone [46]. The 4 patients who developed MDS in the present study had previously been treated with combination chemotherapies including alkylators, epipodophyllotoxins, and/or anthracyclines. Two of these patients (cases 2 and 3) had received radiotherapy as prior therapies, and 2 patients (cases 1 and 3) received radiotherapy after completion of 2-CdA treatment. Considering that these 4 patients had received therapies that are well known to be related to secondary acute myeloid leukemia (AML) or MDS before and after 2-CdA treatment, the direct contribution of 2-CdA is not clear. Because the 2 chromosomal abnormalities of monosomy 7 and deletion of 7q resulting from der(1;7) observed in 2 patients (cases 1 and 2, respectively) are often detected in patients with secondary AML or MDS after exposure to alkylating agents or radiation, whether alkylating agents or radiation had more causative roles than 2-CdA in the development of MDS in these 2 patients would be reasonable to consider. Although Kong et al reported secondary malignancies that appeared during long-term follow-up in previously treated patients with advanced indolent NHL treated with 2-CdA, they also concluded that the contribution of 2-CdA was not clear [29]. Clarifying the role of 2-CdA in the development of secondary AML or MDS requires further investigations, especially in a group of patients with previously untreated indolent NHL.

Despite the definitive activity of 2-CdA against lymphoid malignancies, most patients are destined to relapse. In our study, the estimated median PFSs for all eligible patients and all responders were 239 days and 386 days, respectively. Because purine analogs interfere with DNA repair, their addition to conventional DNA-damaging chemotherapy might augment the tumoricidal effect of the drugs. The combined use of 2-CdA with other cytotoxic agents such as cyclophosphamide and mitoxantrone was reported to be effective against heavily pretreated patients with advanced indolent lymphoid malignancies or mantle cell lymphoma [34,47]. Recently, an anti-CD20 monoclonal antibody (rituximab) has been shown to have high effectiveness against indolent B-cell NHL [48,49]. Because the mechanisms of action and the profiles of toxicity of rituximab are different from those of cytotoxic agents, including 2-CdA, and because a synergistic effect between rituximab and 2-CdA has been reported [50], a clinical trial investigating the combined use of 2-CdA and rituximab seems warranted.

In summary, we have demonstrated in a multi-institutional phase II study the definitive efficacy and acceptable toxicity of 2-CdA with a schedule of continuous intravenous infusion for 7 consecutive days at a dose of 0.09 mg/kg daily for the treatment of patients with refractory or relapsed indolent NHL. Further studies are required to explore the optimal combination chemotherapy regimen for this agent and other antilymphoma drugs as well as to determine a more convenient schedule of infusion.

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Review Article

Treatment of Indolent Non-Hodgkin's Lymphoma with Cladribine as Single-Agent Therapy and in Combination with Mitoxantrone

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Abstract

The term *indolent* in describing a non-Hodgkin's lymphoma (NHL) generally refers to a group of B-cell NHLs composed of predominantly small cells that make up several categories, including follicular lymphoma, small lymphocytic lymphoma, and lymphoma of mucosa-associated lymphoid tissue. Most patients with follicular lymphoma respond to therapy, and the average survival time in large series is approximately 10 years. Patients who achieve a complete remission with initial treatment have an approximately 25% chance of remaining free of disease for 10 years. However, this means that more than 80% of patients will require salvage therapy. Cladribine is a newer purine analogue and is of particular interest because it is resistant to deamination by adenosine deaminase. It is cytotoxic to both proliferating and resting lymphocytes, making it an attractive agent for the treatment of indolent NHL. In this review article, we summarize the current treatment approaches for indolent NHL and the results of cladribine monotherapy studies in Japan and cladribine studies in Germany that have focused on a combination therapy with mitoxantrone. Cladribine is a potent inhibitor of DNA repair. The combination of a DNA-damaging agent with an inhibitor of DNA repair constitutes the rationale for combining cladribine with mitoxantrone. A German study has demonstrated that the combination of reduced-dose cladribine and mitoxantrone is a highly active regimen with favorable toxicity profiles. Cladribine is highly effective as a single agent and in combination with mitoxantrone in the treatment of indolent NHL, and its availability broadens the range of therapeutic options for indolent NHL.
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Key words: Cladribine; 2-CdA; Mitoxantrone; Indolent lymphoma

1. Introduction

The term *indolent* in describing a non-Hodgkin's lymphoma (NHL) generally refers to a group of B-cell lymphomas composed of predominantly small cells that make up several categories in the World Health Organization (WHO) classification of lymphomas [1]. The term *indolent* is imprecise in that it implies that all of the patients in these lymphoma subgroups have slowly progressive disease and long survival times and that patients in other subgroups do not. This is certainly not the case for all patients with follicular lymphoma, lymphoma of mucosa-associated lymphoid tissue (MALT), and small lymphocytic lymphoma (ie, the types of NHL usually considered as indolent). For example, some patients with follicular lymphoma have a high International Prognostic Index (IPI) score [2] and a shorter median survival time than patients with diffuse large B-cell lymphoma—ie, the prototypic aggressive lymphoma—who have a low IPI score [3].

The best approach today for patients with NHL involves determining an accurate histologic diagnosis by using the WHO classification and then using the IPI to assign a prognostic score. The different subgroups in the WHO classification represent entities that are, for the most part, biologically and clinically distinct entities. It is therefore not surprising that the same treatment regimen might not be equally applicable to each disease. Within any particular subtype of NHL, patients with localized disease and a low IPI score are often treated differently than patients with disseminated disease and a high IPI score. The remainder of this article is devoted to a review of the current treatment approaches that have been shown to be effective for each of

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the major types of NHL that are usually lumped together as indolent lymphomas.

2. Follicular Lymphoma

Follicular lymphoma represents 25% to 30% of NHLs in North America and western Europe but a smaller proportion of those in Asia [4]. It is graded according to the proportion of large cells in the tumor into grades I, II, and III [5]. Follicular lymphoma grade III sometimes behaves like a diffuse large B-cell lymphoma, and some of these patients can have long-term, disease-free survival with chemotherapy regimens usually used for diffuse large B-cell lymphoma. For this reason, most physicians consider patients with grade I and grade II follicular lymphoma to have indolent lymphomas. However, as was mentioned earlier, the occasional patient with a high IPI score has a poor prognosis even with grade I or II follicular lymphoma. A wide variety of treatments are active in treating patients with follicular lymphoma. No consensus as to the best treatment approach has developed, and excellent physicians might have widely varying recommendations for the same patient. In asymptomatic patients, close observation without therapy (ie, watch and wait) is an acceptable treatment approach and is often used. Horning and Rosenberg described a group of 83 patients with predominantly follicular lymphoma in whom initial treatment was deferred [6]. These patients were, of course, asymptomatic. At 10 years, 73% of the patients remained alive, and the median time to requiring treatment was 3 years. More than 20% of the patients underwent spontaneous regression while they were being observed without therapy.

Patients with localized follicular lymphoma, although rare, have a particularly good outlook. In this group of patients, involved-field or extended-field radiotherapy has yielded 10-year disease-free survival rates of approximately 50% in several series [7-9]. Two reports described even better results with the combination of chemotherapy and involved-field radiotherapy [10]. However, it should be noted that these patients also had the best results with observation and no initial therapy.

Many treatments have been used in patients with follicular lymphoma who present with disseminated and/or symptomatic disease. Single-agent chemotherapy, usually using chlorambucil, can control symptoms and cause regressions (although usually partial) in a great majority of patients, and patients can often be retreated successfully after relapse [11].

Many combination chemotherapy regimens have been used for patients with follicular lymphoma. These regimens can be grouped into 3 broad categories. The combination of cyclophosphamide, vincristine, and prednisone (CVP) has been widely used and has a high response rate. Combining the same drugs with an anthracycline such as doxorubicin hydrochloride (Adriamycin) is also a popular treatment approach and may benefit subsets of patients. The newest combinations have been based on purine analogues such as fludarabine and cladribine. Purine analogue–based regimens have been demonstrated to be highly active, and there is some hint that they might have a higher complete response (CR) rate than CVP or CHOP (a regimen of cyclophosphamide, hydroxydaunomycin, vincristine [Oncovin], and prednisone).

The addition of the humanized anti-CD20 antibody rituximab has had a major effect on the therapy of patients with follicular lymphoma. Used alone as the initial therapy, rituximab has a CR rate of 50% to 75% and a median response duration of approximately 1 year [12]. The minimal toxicity associated with the use of rituximab has made it particularly popular as a single agent for treating elderly patients [13]. It is now clear that administering maintenance therapy prolongs the remission duration [13,14]. To date, no serious toxicity has resulted from the long-term suppression of circulating B-cells that accompanies the use of rituximab.

Radiolabeled antibodies, also targeted against CD20, have been approved in the United States for use in patients with follicular lymphoma. These antibodies are very active in salvage therapies [15-17] but have been used only occasionally as part of the initial treatment. In 1 large series that used the antibody tositumomab the overall response rate (ORR) was 97%, and 63% of the patients had a complete remission with a 3-year progression-free survival rate of 68%.

The combination of standard chemotherapy regimens with rituximab or radiolabeled antibodies has been increasingly used to treat patients with grade I and grade II follicular lymphoma. A phase II study of CHOP chemotherapy combined with rituximab showed a high CR rate and a median duration of response that exceeded 6 years [18]. A recent study from the United Kingdom showed that the addition of rituximab maintenance therapy to low-dose CVP therapy dramatically prolonged remission duration [19]. Similar results have been reported for fludarabine combinations with the antibody rituximab [20]. Currently, a combination chemotherapy regimen combined with rituximab is used in a high proportion of patients with grade I and grade II follicular lymphoma.

A variety of other treatment approaches have been shown to be active in patients with follicular lymphoma. Interferon α is an active single agent, and there is some data support for the use of this agent in prolonging survival in high-risk patients who receive an anthracycline-containing combination chemotherapy regimen [21]. Lymphoma vaccines are being studied for the treatment of these patients, and phase III trials are currently ongoing. Both autologous and allogeneic bone marrow transplantation can rescue patients with relapsed follicular lymphoma [22-25], and 1 study of autologous transplantation as part of the primary therapy for high-risk patients was particularly encouraging [26]. Several new agents, including the proteasome inhibitor bortezomib and Bcl-2 antisense, are being studied [27,28].

Most patients with follicular lymphoma respond to therapy, and the average survival time in large series is approximately 10 years. Those patients who achieve a complete remission with initial treatment have an approximately 25% chance of remaining free of disease for 10 years. The advent of multiple new treatment approaches suggests that our ability to regularly cure patients with this lymphoma is just over the horizon.

3. Small Lymphocytic Lymphoma/Chronic Lymphocytic Leukemia

Small lymphocytic lymphoma and chronic lymphocytic leukemia (CLL) represent a clinical spectrum of the same

disorders. They are lumped together as 1 disease in the WHO classification. Patients can be divided into those who have disease confined to the blood and bone marrow without cytopenias, those with lymphadenopathy and/or hepatosplenomegaly, and those who have anemia and/or thrombocytopenia. More recently, other prognostic factors have become apparent. Patients with malignancies who have immunoglobulin heavy chain genes that are not rearranged have a poorer prognosis than those who have rearranged immunoglobulin heavy chain genes [29]. More recently, the expression of CD38 and ZAP-70 has been shown to predict treatment outcome [29,30].

These patients frequently, but not nearly always, present with a lymphocytosis and only occasionally with localized disease. Very few cases are appropriately treated with involved-field radiotherapy alone. In the past, the standard treatment for patients with CLL was chlorambucil. However, recent data have demonstrated that purine analogues are, by far, the most active agents. Fludarabine, cladribine, and pentostatin are all highly active drugs. Fludarabine used in combination with cyclophosphamide or mitoxantrone plus rituximab has yielded a complete remission in a high proportion of patients—previously a rare outcome [31]. It appears that cladribine and pentostatin are at least as active as fludarabine, and studies are ongoing with combinations including both agents. As with follicular lymphoma, some older patients may do well with rituximab as a single agent [32].

4. MALT Lymphoma

MALT lymphomas are extranodal small lymphocytic lymphomas that were sometimes referred to as "pseudolymphomas" in the past. These lymphomas are frequently localized at presentation and can often be cured with local therapy [33]. They are seen most frequently in the stomach, lung, salivary gland, thyroid gland, lacrimal gland, orbit, and skin; however, they may appear in essentially any organ. They tend to be slow-growing neoplasms, but approximately 30% are disseminated at diagnosis and follow a course similar to that seen with follicular lymphoma [34,35].

Localized MALT lymphomas can frequently be cured with surgical excision or involved-field radiotherapy [33]. However, MALT lymphomas appearing in the stomach present a special situation. Gastric MALT lymphomas usually occur in association with infection by *Helicobacter pylori*. Patients with localized lymphoma in whom the *H pylori* infection can be eliminated with antibiotic therapy have often been demonstrated to have regression of their lymphoma [36]. Although there is some evidence that minimal residual lymphoma remains [37], it is clear that a long survival time free of recurrence is possible [36]. Patients unlikely to benefit from *H pylori* eradication are those with deep invasion by the tumor and those whose tumors contain the t(11;18) chromosomal translocation [38,39].

NHLs that typically pursue an indolent course represent a significant subset of all these disorders. Patients with localized MALT lymphoma and follicular lymphoma and those patients with disseminated follicular lymphoma who achieve a CR to combination chemotherapy can have prolonged disease-free survival, and some may be cured. Several trials with purine analogue–containing regimens have been reported in the literature, and these regimens show promising activity in the treatment of indolent lymphomas. The advent of the newer purine analogues fludarabine and cladribine broadens the range of therapeutic options for indolent lymphomas, particularly in patients with relapsed disease, and continues to improve our ability to benefit these patients.

5. Cladribine Studies in Japan

Cladribine (2-chlorodeoxyadenosine) is a chlorinated purine analogue that is resistant to adenosine deaminase. Phosphorylated derivatives of cladribine accumulate in lymphocytes with high deoxycytidine kinase activity, resulting in DNA strand breaks and cell death [40-42]. Several clinical trials have shown definite clinical activity of cladribine against B-cell malignancies, such as hairy cell leukemia (HCL) [43,44], B-cell CLL [45,46], B-cell prolymphocytic leukemia [47], and indolent B-cell NHL [48-50].

5.1. Japanese Phase I and Pharmacologic Study of Cladribine

In a study to clarify the toxicity profiles of cladribine in Japanese patients, a phase I and pharmacologic study of cladribine was conducted with a schedule of 7-day continuous intravenous (IV) infusion every 28 days [51]. Cladribine was supplied by Janssen Pharma, Tokyo, Japan, as a 0.1% (1 mg/mL) solution of endotoxin-free cladribine in sterile 0.9% sodium chloride.

In the literature from Western countries, the recommended phase II dose of cladribine with a schedule of 7-day continuous IV infusion was reported to be 0.1 mg/kg per day. However, as Beutler described in his review article, the actual dose of cladribine that had been administered was found to be only 87% of the amount stated after the drug concentration had been standardized by using the extinction coefficient of chloroadenine [40]. Therefore, in the subsequent Japanese studies, the recommended phase II dose that had been established in Caucasian patients was judged to be 0.09 mg/kg per day with a schedule of 7-day continuous IV infusion.

The appropriate starting dose of cladribine was based on the results of the previously reported clinical trials in Western countries and determined to be 0.06 mg/kg per day (level 1), and dose escalations in increments of 0.03 mg/kg per day were planned up to 0.15 mg/kg per day (level 4). Intrapatient dose escalation was not allowed. The treatment was repeated every 28 days unless patients developed progressive disease or dose-limiting toxicities (DLTs). In this study, the DLTs were defined as grade 4 hematologic toxicity and/or nonhematologic toxicity of grade 3 or greater, according to the toxicity grading criteria of the Japan Clinical Oncology Group [52], which is an expanded version of the National Cancer Institute Common Toxicity Criteria.

Daily administration of granulocyte colony-stimulating factor was planned when neutrophil counts decreased to less than 1000/μL. Three patients were scheduled for entry at each dosage level. If each of the above-mentioned DLTs was observed in 1 of the 3 patients, an additional 3 patients were

scheduled for treatment at the same dosage level. The maximum tolerated dose was defined as the dosage level at which DLTs were observed in 2 or more of the 3 to 6 patients.

Ten previously treated patients with various lymphoid malignancies were enrolled, with 3 patients enrolled at level 1 and 7 at level 2. No DLT was observed in the 3 patients who received 0.06 mg/kg per day (level 1). Of the 7 patients who received 0.09 mg/kg per day (level 2), 1 patient developed grade 4 hypoxemia and grade 4 thrombocytopenia at the third cycle, and another developed grade 4 neutropenia at the first cycle. Neither neurotoxicities nor serious infectious complications were observed.

After the first course of cladribine in all 6 patients (3 patients each at level 1 and level 2), an independent monitoring committee was convened. At that point, no DLTs had occurred among the 6 enrolled patients. On the basis of the data of this study and the publications from the United States, the independent monitoring committee recommended that an additional 4 patients be treated at level 2 and that the dose of cladribine not be escalated further. In particular, we took the warning about the neurotoxicity of purine analogues by Cheson et al [53] into consideration and stopped any further dose escalation to avoid the occurrence of severe or irreversible neurotoxicity.

Of the 6 eligible patients who were treated at level 2, 1 patient with mantle cell lymphoma, 1 with CLL, and 1 with adult T-cell leukemia-lymphoma (ATL) attained objective responses.

Blood was sampled before initiating the infusion of cladribine (0 hour), at 23, 47, 71, and 143 hours during the continuous IV infusion, and at 2, 4, 6, 9, 24, and 48 hours after the end of the 7-day continuous IV infusion. The concentration of cladribine in the plasma was determined by liquid chromatography/mass spectrometry with a limit of detection of 0.1 ng/mL. The area under the concentration-versus-time curve (AUC) was calculated according to the trapezoid rule from time 0 to the last measurable concentration and extrapolated to time infinity. The elimination half-life of cladribine in plasma was calculated by log-linear regression of the points considered to be in the terminal phase.

The analysis of the 7 patients without leukemic cells showed that their AUCs for plasma cladribine increased in a dose-dependent manner from 2661.3 ± 300.4 nM · hours at level 1 (n = 3) to 3411.3 ± 341.0 nM · hours at level 2 (n = 4) (P = .034). In addition, a tendency for the maximum concentration and the steady state concentration values to increase with the cladribine dose was recognized. We analyzed whether pharmacokinetic parameters such as AUC and maximum concentration were correlated with the toxicity or response observed in this study; however, no correlation was found. The plasma concentrations of cladribine in the 4 patients treated at level 2 (excluding the 2 highly leukemic patients [cases 5 and 9]) are shown in Figure 1.

In conclusion, the recommended phase II dosage of cladribine (0.09 mg/kg per day as a 7-day continuous IV infusion) determined for Caucasian patients can be safely administered to Japanese patients. These encouraging results prompted us and other Japanese investigators to plan subsequent phase II studies of therapy against ATL, HCL, and indolent NHL [51].

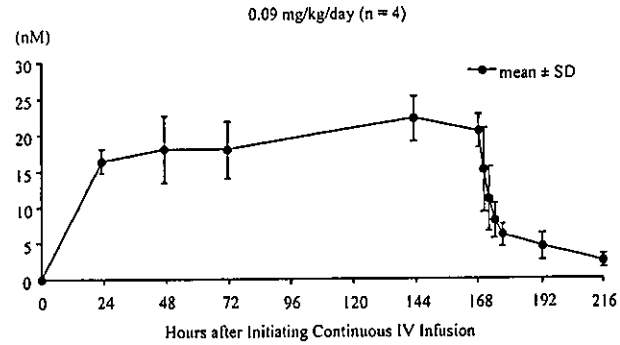

Figure 1. Plasma concentration of cladribine in the 4 patients treated at level 2 (0.09 mg/kg per day by 7-day continuous intravenous infusion), excluding the 2 highly leukemic patients. Data are expressed as the mean ± SD. Reprinted from [51] with permission.

5.2. Phase II Study of Cladribine for ATL

ATL is a retrovirus-associated peripheral T-cell malignancy with an extremely poor prognosis. The median survival time of patients with acute or lymphoma-type ATL treated with various combination chemotherapies is less than 1 year [54]. Cladribine shows definite clinical activity against various lymphoid malignancies, including cutaneous T-cell lymphoma [55-57]. An in vitro study showed the sensitivity of T-lymphoblastoid cell lines to cladribine [58]. The therapeutic efficacy of cladribine for ATL was evaluated in a multicenter phase II study conducted in Japan [59]. The plan was to administer cladribine to 30 ATL patients at 0.09 mg/kg per day by 7-day continuous IV infusion every 28 days for up to 3 treatment courses.

Until the planned interim analysis, 15 of the 16 enrolled patients with relapsed or refractory ATL were eligible. The clinical characteristics of the 15 eligible patients and the responses to cladribine are shown in Table 1 [59]. Only 1 of the 15 eligible patients showed an objective response (ORR, 7%; 90% confidence interval [CI], 0%-28%), whereas 11 patients (73%) showed progressive disease, mostly during the first treatment course. Because the upper limit of the 90% CI of the ORR did not reach 30% in the interim analysis, the study for ATL was terminated early according to the recommendations by the independent monitoring committee.

In conclusion, cladribine showed objective responses in a fraction of ATL patients; however, the role of cladribine in the treatment of ATL is limited with this dose and schedule [59].

5.3. Phase II Study of Cladribine for Relapsed or Refractory Indolent NHL

The primary purpose of this multicenter phase II study was to determine the efficacy and safety of cladribine for Japanese patients with refractory or relapsed indolent NHL [60]. Previously treated patients with indolent NHL were eligible if they met the following criteria: (1) histologic and/or cytologic confirmation of indolent NHL categorized as

Table 1.
Characteristics of 15 Eligible Patients and Their Responses to Cladribine [59]*

Case No.	Age, y/Sex	Subtype	Disease Status	PS	Prior Regimens, n	Other Prior Therapies	Assessable Lesions	Cladribine Courses, n	Response
1	66/M	Lymphoma	Resistant relapse	1	5	None	LNs, LDH	2	NC
2	50/F	Acute	Primary resistant	3†	1	None	PB, liver, LDH	1	PD
3	63/F	Acute	First relapse	0	1	None	PB, LDH	2	PD
4	71/M	Acute	Resistant relapse	2	2	None	PB, LNs, LDH	1	PD
5	60/M	Acute	Primary resistant	0	2	None	PB	3	NC
6	43/F	Lymphoma	First relapse	1	1	None	LNs	2	NC
7	48/F	Lymphoma	First relapse	0	1	None	LNs, skin, LDH	1	PD
8	48/F	Acute	Resistant relapse	2	5	None	LNs, liver, skin, LDH	3	PR
9	69/M	Acute	Primary resistant	1	2	RT, IFN-α	PB, LNs, skin, LDH, PE, hypercalcemia	1	PD
10	58/M	Lymphoma	First relapse	1	1	RT	PB, LNs, skin, LDH	1	PD
11	47/M	Acute	Primary resistant	1	1	None	PB, LDH	1	PD
12	59/F	Acute	Primary resistant	2	1	None	PB, LNs, skin, LDH	1	PD
13	40/M	Acute	Primary resistant	0	5	None	LNs, skin	1	PD
14	68/F	Lymphoma	Primary resistant	1	1	None	PB, LNs, LDH, head tumor	1	PD
15	46/F	Lymphoma	Resistant relapse	2	1	None	PB, LNs, PE, ascites, LDH, hypercalcemia	1	PD

*PS indicates performance status; LNs, lymph nodes; LDH, lactate dehydrogenase; PD, progressive disease; PB, peripheral blood; NC, no change; PR, partial response; RT, radiotherapy; IFN-α, interferon α; PE, pleural effusion.

†In Case 2, the PS at the time of registration was 2 but was 3 at the start of cladribine administration because of rapid disease progression. This case was judged eligible by the extramural review.

peripheral B-cell neoplasms numbered 1 to 5 or as mycosis fungoides by the revised European-American classification of lymphoid neoplasms; (2) patients who have NHL refractory to conventional chemotherapy, have relapsed after attaining a CR, or show disease progression after attaining a partial response (PR); (3) no chemotherapy or irradiation within 2 weeks prior to the study; (4) a life expectancy of at least 8 weeks; (5) an age ≥15 years and <75 years; (6) a performance status of 2 or better according to the Eastern Cooperative Oncology Group scale; (7) adequate bone marrow function, adequate hepatic function, adequate renal function, adequate pulmonary function, and a normal electrocardiogram; and (8) written informed consent given.

5.3.1. Patient Characteristics

Forty-five patients with relapsed or refractory indolent NHL were enrolled in the Japanese multicenter phase II study. The central pathology review revealed that 41 patients with indolent B-cell lymphoma (34 with follicular lymphoma, 4 with mantle cell lymphoma, and 3 with marginal zone B-cell lymphoma) and 2 patients with mycosis fungoides were eligible. The median number of prior chemotherapy regimens was 2 (range, 1-14). Cladribine was given by continuous IV infusion at a dosage of 0.09 mg/kg per day for 7 consecutive days and repeated every 28 days up to the maximum of 6 cycles.

5.3.2. Results and Toxicity

The median number of administered cycles of cladribine was 3 (range, 1-6). The ORR was 58% (95% CI, 45%-71%) with 14% CR (95% CI, 6%-26%). The progression-free rates at 2 years for all 43 eligible patients and all 25 responding patients were 30% and 48%, respectively. The median time to progression for the 25 responders was 9 months (range, 1-31+ months). Neutropenia and thrombocytopenia of grade 3 or greater were observed in 53% and 38% of patients, respectively. Prolonged (180 days or longer) neutropenia and/or thrombocytopenia of grade 3 or greater were observed in 27% of the patients and persisted up to 419+ days. Five patients developed infections of grade 3 or greater, including 2 treatment-related deaths (systemic herpes simplex virus infection and pulmonary aspergillosis). The other nonhematologic toxicities were acceptable. Four patients developed myelodysplastic syndrome (MDS) at 13 months to 2 years after the completion of cladribine treatments.

5.3.3. Secondary Malignancies

Because purine analogues induce profound and prolonged immunosuppression, there has been a concern about the potential for the development of a secondary malignancy. However, Cheson et al conducted a study to assess the frequency of second tumors in CLL patients treated with fludarabine (n = 724) and in HCL patients treated with pentostatin (n = 409) and cladribine (n = 979) [61] and concluded that nucleoside analogues can be safely administered to patients with CLL or HCL without a significantly increased risk of secondary malignancies. However, their conclusion regarding the use of cladribine in HCL patients is difficult to extrapolate directly to indolent NHL patients for the following reasons: First, the number of cladribine treatment cycles used in HCL patients is generally 1, in contrast to multiple cycles used in treating indolent NHL patients. Second, HCL patients are mostly previously untreated at the time of

cladribine treatment, in contrast to the mostly previously treated indolent NHL patients. All of the 4 patients who developed MDS in this study had received alkylating agents, epipodophyllotoxins, and/or anthracyclines. In addition, 2 patients had received radiotherapy before cladribine treatment, and 2 patients received it afterwards. Thus, the relationship between cladribine and MDS in the 4 cases in this study is not clear.

We concluded that cladribine is an active agent in the treatment of relapsed or refractory indolent NHL with durable major responses. Toxicity was acceptable in most patients. However, prolonged myelosuppression and the potential for the development of MDS, especially in heavily pretreated patients, should be carefully monitored in addition to monitoring for opportunistic infections due to immune suppression [59].

In 2002, cladribine was approved for the treatment of HCL and indolent B-cell NHL by the Ministry of Health, Labor and Welfare of Japan. Cladribine has a definite role in the treatment of indolent lymphoid malignancies. Further investigations are warranted.

6. Cladribine Studies in Germany

6.1. Single-Agent Therapy

In a previous study conducted in Germany, we evaluated the efficacy as well as the toxicity of cladribine therapy as an intermittent 2-hour infusion over 5 days as first-line therapy in a cohort of patients with advanced indolent NHL [62]. In this study, patients were eligible if they had a histologically confirmed diagnosis of a follicular, small lymphocytic lymphoma or marginal zone lymphoma.

6.1.1. Cladribine: Treatment Schedule

In most studies, cladribine was administered as a continuous infusion for 7 days [48,49,63,64]. Cladribine can also be administered as an intermittent 2-hour infusion [65], which is as safe and as effective as a continuous infusion but is without the problems associated with this mode of administration [66,67].

Cladribine was administered in our study at a dosage of 5 mg/m^2 per day over 5 consecutive days by a 2-hour infusion. This treatment was repeated every 4 to 5 weeks for a maximum of 6 cycles. Prophylactic antibiotic treatment, including prophylaxis for *Pneumocystis carinii* pneumonia, was not given.

6.1.2. Cladribine: Results

Forty-nine untreated patients were evaluable for toxicity and response. The ORR was 86% (95% CI, 73%-94%), and the CR rate was 43% (95% CI, 29%-58%). Only 7 patients achieved no response. The median remission duration was 19 months. Patients with follicular and small lymphocytic lymphomas showed high response rates of 96% and 88%, respectively. The CR rate for patients with follicular lymphomas was considerably high at 57% (95% CI, 34%-77%).

6.1.3. Toxicity of Cladribine as Single-Agent Therapy

Nonhematologic toxicity was generally mild and mainly restricted to WHO grades 1 and 2. Nausea, vomiting, and alopecia were not observed. There were no treatment-related deaths. Granulocytopenia was the most common side effect noted, with grade 3 granulocytopenia occurring in 42 (14%) and grade 4 occurring in 10 (3%) of all evaluable cycles. One case of bacterial pneumonia during a granulocytopenic phase and 5 localized herpes zoster infections have been observed. No other severe or opportunistic infections were observed. Grade 3 or 4 thrombocytopenia was rather rare and occurred in only 5 (2%) of all evaluable cycles. Three patients developed polyneuropathy, with 2 patients developing mild and reversible peripheral dysesthesia and 1 patient experiencing a demyelinating polyneuropathy with consequent weakness of the legs, which resolved 18 months after cessation of therapy. One patient had reactivated tuberculosis that was treated successfully. The levels of CD4$^+$ lymphocytes, which were at a median of 570/μL before treatment, decreased to 302/μL after 2 cycles, 188/μL after 4 cycles, and 145/μL after 6 cycles. The CD4$^+$ cell counts were measured 12 months and 24 months after the cessation of therapy and showed sustained depression with median values of 195/μL and 324/μL, respectively. There was no correlation between CD4$^+$ cell counts and infectious complications.

A 68-year-old female patient who was in CR for 9 months after the cessation of therapy died from meningitis, which was suspected to be a cerebral listeriosis. Eight months after receiving 2 cycles of cladribine, a 69-year-old male patient developed a squamous cell carcinoma at the lobe of the left ear that was extirpated *in sano*. No other significant infections have been seen since the cessation of therapy after a stable response was reached or during the period when a salvage therapy had to be initiated for a recurrence.

6.1.4. Cladribine as Single-Agent Therapy: Conclusion

Until recently, the recommended mode of cladribine administration has been continuous infusion for 7 days. Pharmacokinetic studies have shown that the half-life of intracellular nucleotides is very long and that the AUCs of cladribine in the plasma and the concentrations of intracellular 2-chlorodeoxyadenosine nucleotides were similar after intermittent 2-hour infusion and after continuous infusion [65]. This result prompted us to use intermittent 2-hour infusion for 5 days to make the treatment more convenient for outpatients. From our results we conclude that the administration of cladribine by intermittent 2-hour infusion for 5 days appears to be as effective as a continuous-infusion regimen for 7 days, demonstrating that clinical efficacy is in agreement with the pharmacologic data [62]. Cladribine treatment is simplified with the 2-hour infusion schedule, and this intermittent schedule can be generally recommended.

The results corroborate the high activity of cladribine in the treatment of advanced low-grade lymphomas. The therapeutic efficacy seems to be comparable to that of combined chemotherapy regimens. Because of the low incidence of myelotoxicity and organ toxicity as well as the absence of side effects such as vomiting and alopecia, the use of cladrib-

ine as first-line treatment should not be a matter of debate. The observed long-lasting immunosuppressive effect may contribute to late toxicities such as secondary malignancies, as described for HCL patients treated with cladribine [68]. We observed 1 secondary neoplasm in our study, and this single case may be in accordance with the small but statistically significant increased risk of secondary cancers observed in HCL patients treated with cladribine [61], although it remains unclear whether this observation is due to the prolonged immunosuppression induced by cladribine or is due to a possible predisposition of patients being at a greater risk for secondary cancers because of their malignant disease [69]. No cases of secondary MDS were observed.

Yet, no single agent is likely to have a substantial effect on the survival of patients with an indolent lymphoma. Recent studies, therefore, have focused on combining purine analogues with other agents active against these lymphoma entities. Because of their low nonhematologic toxicities, purine analogues can be easily included in multiagent regimens. Using this rationale, we demonstrated in a preclinical study the synergistic effects of cladribine and mitoxantrone on the induction of apoptosis of lymphoma cells in vitro [70].

6.2. Cladribine in Combination with Mitoxantrone

Saven et al were the first to show in a dose-escalation study that cladribine can be combined with mitoxantrone in the treatment of indolent NHL. They used a full-dosage cladribine schedule of 0.1 mg/kg per day for 7 days by continuous infusion [71]. Other investigators proposed a reduced dosage of cladribine as an appropriate method to reduce toxicity while maintaining the antitumor activity of standard-dosage cladribine [72,73]. On the basis of the results of these studies and the potential synergy between cladribine and mitoxantrone, we reduced the dosage of cladribine in the subsequent German study, administering it on 3 days only at 5 mg/m^2 as a 2-hour infusion.

In this study, patients with a follicular, lymphoplasmacytoid (Waldenström macroglobulinemia), or marginal zone lymphoma were eligible. Patients were required to have received no prior chemotherapy, to have had a first relapse after pretreatment with radiotherapy, or to have undergone 1 chemotherapy regimen not containing purine analogues.

6.2.1. Cladribine plus Mitoxantrone: Treatment Schedule

Cladribine was administered at a dosage of 5 mg/m^2 per day over 3 consecutive days by 2-hour IV infusion. Mitoxantrone was given at a dosage of 8 mg/m^2 per day on days 1 and 2 for untreated patients or at a dosage of 12 mg/m^2 per day on day 1 for patients in a first relapse. The treatment was repeated every 4 to 5 weeks for a maximum of 6 cycles.

6.2.2. Cladribine plus Mitoxantrone: Results

The median age of the 62 evaluable patients was 59 years (range, 31-76 years). Eleven patients had stage IIIA disease, 6 patients had stage IIIB disease, and 45 had stage IV disease. Forty-two patients were previously untreated, and 20 patients entered the study in their first relapse. Pretreatment consisted of CHOP or CHOP-like regimens in 8 cases, COP (cyclophosphamide, vincristine [Oncovin], and prednisone) regimens in 4 cases, chlorambucil plus prednisone in 4 cases, and radiotherapy in 4 cases. The characteristics of the 62 patients assessable for response and toxicity are summarized in Table 2.

Table 2.
Patient Characteristics: Cladribine plus Mitoxantrone*

Patients (male/female), n	62 (34/28)
Median age (range), y	59 (31-76)
Stages, n	
III (A, B)	17
IVA	22
IVB	23
Prior therapy, n	
Untreated	42
First relapse	20
Histology (untreated/pretreated), n	
Follicular	32 (26/6)
Mantle cell	18 (9/9)
Lymphoplasmacytoid	9 (4/5)
Marginal zone (MALT)	2 (2/0)
Unclassifiable low-grade B-cell	1 (1/0)
Prognostic factors, n	
Performance status >2	0
Extranodally involved sites >1	14
LDH >200 U/L	30
Age >60 y	28
Stage III or IV	62
β_2-Microglobulin >2.0 mg/dL, n†	29
B-symptoms, n	28
Bone marrow involved, n	28
Gastrointestinal tract involved, n	8
Bulky disease (>5 cm), n	31
Prognostic groups (IPI), n	
Low risk (1 risk factor)	18
Low intermediate risk (2 risk factors)	26
High intermediate risk (3 risk factors)	15
High risk (4-5 risk factors)	3

*MALT indicates mucosa-associated lymphoid tissue; LDH, lactate dehydrogenase; IPI, International Prognostic Index.
†Data evaluable for 43 patients.

Overall, 285 cycles of therapy were applied with a median of 5 cycles to each patient (range, 1-6 cycles). The ORR in the entire group of 62 assessable patients was 90% (95% CI, 80%-96%) with a CR rate of 44% (95% CI, 31%-57%) and a PR rate of 47% (95% CI, 34%-60%) (Table 3).

The median remission duration was 25 months (range, 6-42+ months). Thirty-one patients have relapsed to date after 6 to 38 months (Figure 2). There was no correlation between response and elevated β_2-microglobulin level (P = .10) or elevated lactate dehydrogenase level (P = .18). There was no statistical difference in the durations of relapse-free survival between the CR and PR patients (25 months and 24 months, respectively; P = .25) or between the previously untreated and pretreated patients (31 months and 21 months, respectively; P = .09). The ORR was 88% (95% CI, 74%-96%) for the 42 untreated patients and 95% (95% CI, 75%-100%) for the 20 pretreated patients, with only 1 pretreated patient not responding to therapy.

Table 3.
Treatment Results: Cladribine plus Mitoxantrone*

Entity	Patients, n	CR, n (%)	PR, n (%)	CR + PR, n (%)	Median Remission, mo	OS at 36 mo, %
Follicular	32	15 (47)	11 (34)	26 (81)	29	87
Previously untreated	26	10 (38)	11 (42)	21 (81)	—	—
Pretreated	6	5 (83)		5 (83)	—	—
Mantle cell	18	8 (44)	10 (56)	18 (100)	24	68
Previously untreated	9	3 (33)	6 (67)	9 (100)	—	—
Pretreated	9	5 (56)	4 (44)	9 (100)	—	—
Lymphoplasmacytoid	9	1 (11)	8 (89)	10 (100)	—	—
Previously untreated	4		4 (100)	4 (100)	—	—
Pretreated	5	1 (20)	4 (80)	5 (100)	—	—
Marginal zone, previously untreated	2	2		2 (100)	—	—
Unclassifiable low-grade B-cell	1	1			—	—
All previously untreated	42	16 (38)	21 (50)	37 (88)	31	82
All pretreated	20	11 (55)	8 (40)	19 (95)	21	71
Total (all patients)	62	27 (44)	29 (47)	56 (90)	25	80

*CR indicates complete response; PR, partial response; OS, overall survival rate; —, statistical tests not done because of low statistical power of the small numbers of patients.

The ORR for 9 patients with lymphoplasmacytoid lymphomas (Waldenström macroglobulinemia) was 100% (95% CI, 66%-100%), and 26 of 32 patients with follicular lymphomas responded to mitoxantrone for a response rate of 81% (95% CI, 64%-93%) (Table 3).

In 9 responding patients, therapy was stopped prematurely after 2 or 3 courses, and only 2 of these patients achieved a CR. Twenty-two patients received 2 to 4 courses, and 34 patients received 5 or 6 cycles, with the 2 groups achieving CR rates of 32% and 56%, respectively. The relapse-free survival rates for the 2 groups were not different, whereas the overall survival rates differed significantly ($P = .02$) with a hazard ratio of 4.1 in favor of the patients who received 5 or 6 courses of mitoxantrone therapy.

The overall survival curve for all patients is shown in Figure 3. The median duration of survival has not yet been reached, and the actuarial survival rate at 48 months is 80%. Forty-four patients (71%) were in the group of low or low-intermediate risk when IPI scoring was applied for NHL, and 18 patients (29%) were in the group of high-intermediate or high risk [2]. The overall survival rates of the 2 risk groups were significantly different ($P = .0007$) with a hazard ratio of 6.1, which means that the patients in the higher-risk group die on average at 6 times the rate of patients in the group with the lower risk. Survival differences in univariate analyses were statistically significant for age ($P = .011$), not quite significant for lactate dehydrogenase level ($P = .059$), and not statistically significant for β_2-microglobulin level ($P = .36$). The difference in the durations of overall survival between CR patients and PR patients was statistically significant ($P = .027$), whereas the difference between previously untreated and pretreated patients was not statistically significant ($P = .093$).

6.2.3. Toxicity of Cladribine plus Mitoxantrone

Nonhematologic toxicity was generally mild and mainly restricted to WHO grades 1 and 2 (Table 4). Only 2 patients experienced grade 3 alopecia. One patient had a deep venous thrombosis, which was treated successfully. There were no treatment-related deaths. Granulocytopenia was the most common side effect noted. Grade 3 granulocytopenia occurred in 66 (23%) of 285 evaluable cycles, grade 4 occurred in 142 (49%), and a median granulocyte nadir occurred on day 12. There was no evidence of cumulative myelosuppression for granulocytes except for 1 patient. Also observed were 2 cases of bacterial pneumonia during a gran-

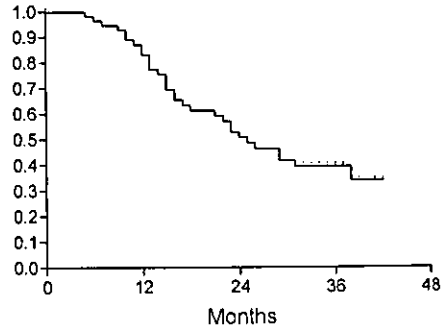

Figure 2. Relapse-free survival for all patients treated with cladribine plus mitoxantrone entering a complete response or a partial response (Kaplan-Meier method).

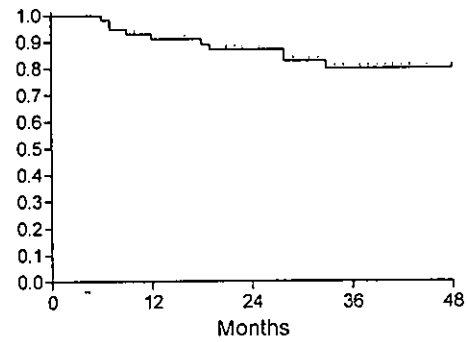

Figure 3. Overall survival for all patients treated with cladribine plus mitoxantrone (Kaplan-Meier method).