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The Multicenter Trial SAKK 37/95 of Cladribine, Cyclophosphamide and Prednisone in the Treatment of Chronic Lymphocytic Leukemias and Low-Grade Non-Hodgkin's Lymphomas

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Key Words
Cladribine · Cyclophosphamide · Leukemia · Lymphoma · Prednisone

Abstract
A multicenter trial was performed to confirm the therapeutic efficacy and the toxicity profile of the combination of cladribine, cyclophosphamide and prednisone in low-grade non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukemia (CLL). Twenty-three adults with previously treated (61%) or untreated (39%) NHL International Working Formulation A or Binet B and C CLL were administered cladribine 0.1 mg/kg/day as a subcutaneous bolus for 5 days, intravenous cyclophosphamide 500 mg/m^2 on day 1, and oral prednisone 40 mg/m^2 on days 1–5, every 4 weeks. Unexpected early hematological toxicities led to dose modifications for pretreated patients who received cladribine for 3 days only up to a maximum of five courses. Responses were observed in 75%, with 7 patients obtaining a complete clinical and hematological response. Median duration of complete response was 9 months. Median time to progression or relapse was 31 months. Myelosuppression and infections were dose limiting whereas posttreatment complications, including fatalities, resulted from infections. Median overall survival time from trial entry was 60 months. Activity of the combination of cladribine, cyclophosphamide and prednisone was confirmed. However, in the specific setting of a multicenter trial, unexpected fatal infectious episodes occurred in pretreated patients. Great caution is thus required in these susceptible patients and the routine use of corticosteroids should probably be abandoned.

Introduction

Chronic lymphocytic leukemia (CLL) and low-grade non-Hodgkin's lymphoma (NHL) are indolent B-cell lymphoproliferative disorders that are usually left untreated at the early stages. Treatment of advanced stages with oral chlorambucil or cyclophosphamide or a multidrug regimen including doxorubicin rarely achieves complete remission (CR) and has never resulted in prolonged relapse-free survival or increased survival [1, 2].

Over the last decade, the purine analogues cladribine and fludarabine have been successfully introduced in clinical practice [3–6]. These drugs are active in both resting and proliferating lymphocytes by inducing apoptosis and by inhibiting the complex mechanisms of DNA repair [7]. Like other compounds of this family, cladribine (2-chloro-2′-deoxyadenosine) is activated by deoxy-

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cytidine kinase and is resistant to deamination by adenosine deaminase.

Cladribine was initially reported to induce CR after one single course of treatment in hairy cell leukemia [8]. Cladribine was also used in previously treated CLL and recurrent or refractory low-grade NHL, achieving an overall response rate of 32–45% [9–11]. Cladribine was then introduced in first-line therapy for CLL achieving an overall response rate of 70–88% and a CR rate of 28–45% [12, 13].

On the other hand, in vitro additive activity was demonstrated when purine analogues were combined to anthracyclines or alkylating agents [14, 15]. The clinical exploitation of this combination resulted in an increase in both complete and overall response rates in previously untreated patients [1, 14, 16].

Based on our own favorable experience of the combination of cyclophosphamide, prednisone and cladribine in a mixed group of pretreated and non-pretreated patients with CLL and NHL [4], we prospectively evaluated this drug combination in a multicenter phase ll trial within the Swiss Group for Clinical Cancer Research (SAKK) lymphoma group.

Patients and Methods

Patients

Eligibility criteria included the following well-established historical classification: confirmed diagnosis of CLL Binet stage B or C or small lymphocytic malignant NHL International Working Formulation A, stage III–IV, obtained within 2 weeks prior to trial entry; age 18–75 years; WHO performance status ≤ 2; negative HIV serology; informed consent according to local policy; life expectancy >3 months; no life-threatening concomitant disease; normal serum creatinine; ASAT, alkaline phosphatase or bilirubin <2× normal value; leukocyte count $>3 \times 10^9$ cells/l, neutrophil count $>1 \times 10^9$ cells/l, thrombocyte count $>100 \times 10^9$ cells/l (unless clearly related to either CLL or NHL). Previous treatment with purine analogs was permitted. Diagnosis was established by both cytological and immunological studies of lymph nodes, blood smears and bone marrow aspirates and centrally reviewed by an expert committee. Pretreatment evaluation included medical history, physical examination, chest radiography and abdominal computerized tomography. This trial was approved by the SAKK scientific committee and by the local ethics committee of each participating institution (n = 8). Every patient gave written informed consent.

Treatment

Cladribine was supplied free of charge to the SAKK by Lipomed (Arlesheim, Switzerland) as a 0.1% solution of 1 mg/ml of cladribine in 0.9% sterile sodium chloride in 10-ml vials. Cyclophosphamide and prednisone were purchased from commercial sources.

Initial Treatment Plan. Cladribine 0.1 mg/kg per day was given subcutaneously for 5 consecutive days together with 500 mg/m^2 of intravenous cyclophosphamide on day 1 and oral prednisone 40 mg/m^2 per day on days 1–5. Courses were given every 28 days until progression or up to a maximum of six cycles. Patients attended the clinic once weekly, with a full blood count and other tests as appropriate. In case of WHO hematological grade 4 toxicity on days 8, 15 or 21 of the previous cycle, cladribine was decreased to 4 or 3 days of treatment. In case of neutrophil count $<1 \times 10^9$/l or thrombocyte count $<100 \times 10^9$/l on day 29, the next treatment was delayed for up to 4 weeks. In case of no recovery, treatment was stopped and the patient was taken off trial treatment and followed for failure, overall survival and toxicities. Colony-stimulating factors were not routinely prescribed, and neither antibiotics nor antiviral prophylaxis were given. No restrictions were made about the use of radiotherapy. Irradiated red blood cells or thrombocytes were given whenever indicated [17]. Adverse reactions were considered acute if occurring from day 1 of the first course until 4 weeks after the end of the last course and late reactions if occurring >4 weeks after the end of the last course.

Revised Treatment Plan. Because 5 out of the first 7 pretreated patients developed unexpected hematological and infectious toxicities after the first or the second course, an amendment to the trial was issued. Subsequently, pretreated patients received cladribine for 3 days only and the maximum number of cycles for both pretreated and non-pretreated patients was reduced to 5.

Response Criteria for CLL

The criteria of the International Workshop on CLL were adopted [18]. CR was defined as no evidence of clinical disease, absence of constitutional symptoms, resolution of lymph nodes, hepatomegaly or splenomegaly, lymphocyte count $<4 \times 10^9$/l, neutrophil count $>1.5 \times 10^9$/l, and bone marrow aspirate and biopsy within normal limits. Partial remission (PR) was defined as a change from stage C to stage A or B, or from stage B to A. Stable disease was defined as no change in the stage of the disease. Progressive disease was defined as a change from stage A to B or C or from stage B to C. Relapse after CR was defined as recurrence of lymph nodes, hepatosplenomegaly or lymphocytosis.

Response Criteria for NHL

CR was defined as the disappearance of known disease on physical examination, chest X-ray, abdominal CT scan, bone marrow biopsy and aspirate (if previously involved), and disappearance of the M-protein by serum immunofixation determined by two observations >4 weeks apart. PR was defined as >50% reduction in measurable disease sustained by >50% decrease in serum M-protein. Any other response was designated as no change. Relapse was defined as an increase in serum M-protein >25% above the lowest value, reappearance of lymph nodes or new lesions.

Response Evaluation Schedule

Patients were evaluated using the same diagnostic and imaging techniques at maximum response and monthly for 3 months, then every 3 months during 18 months, then every 6 months until disease progression. Survival and time to progression or relapse were estimated from day 1 of the treatment according to Kaplan-Meier [19].

Sample Size

The sample size was calculated for the response (CR+PR) rate using the optimal two-stage design. A response rate of 60% was considered uninteresting and one of 80% promising. For a significance level of 5% and 90% power, the required sample size was 26 patients at stage 1 and 19 additional patients at stage 2. If 15 or less patients responded at stage 1, then the trial would be stopped with the conclusion that the trial treatment was uninteresting.

Results

Patient Characteristics

The trial was stopped early due to slow accrual. Between December 1995 and April 1998, 23 patients from eight different institutions participated in the trial (table 1). Two were subsequently excluded after central review of slides (1 mantle cell lymphoma and 1 low-grade lymphoplasmocytic lymphoma, International Working Formulation C), and 1 patient refused treatment. Minor protocol violations were recorded, e.g. diagnostic histology not within the 2-week limit (1 patient) and prednisone omission due to concomitant diabetes (1 patient). Median time from initial diagnosis to treatment was 29 months (range 0.3–144 months). Thirteen patients were male, and median age was 59 years (range 41–73 years). Nine patients had B symptoms, 17patients had CLL (9 Binet stage B and 8 Binet stage C) and 7 had stage IV NHL-A (for 1 non-pretreated patient, both CLL Binet stage C and stage IV NHL-A were recorded; this patient was one of the two who were excluded after slide revision). Fourteen patients were previously treated with chemotherapy such as CVP, chlorambucil and prednisone or purine analogues. Two patients had been splenectomized and 1 had received immunotherapy. Eight patients had hepatomegaly, 13 splenomegaly and 2 had other extranodal involvement (testis and esophagus).

A total of 77 courses of treatment were administered to 22 patients: thirty-eight 3-day courses and thirty-nine 5-day courses. Five patients received one single course, 4 patients received two courses, 3 patients received three courses, 5 patients received five courses and 5 patients received six courses.

Treatment was interrupted in three courses, respectively, due to revision of histology (course 1), thrombocytopenia (course 5) and a serious adverse event (course 2). Twelve courses were delayed because of thrombocytopenia (n = 5), leukopenia together with unspecified infection (n = 1), erysipelas (n = 1), dental abscess (n = 1), chickenpox (n = 1), patient's holiday (n = 1), pneumonia (n = 1) and unspecified infection (n = 1).

Table 1. Patient characteristics (n = 23)

Characteristics	Pre-treated	Non-pretreated
Median age, years (range)		
At diagnosis	57 (48–71)	
At study entry	59 (51–73)	
Sex		
Males/females	15/8	
Previous treatment		
None	10	
Splenectomy	2	
Radiotherapy	1	
Immunotherapy	1	
Chemotherapy	13	
Diagnosis		
CLL	9	7
NHL-A (stage IV)	4	3
Hb, g/dl		
Median	12.1	11.7
Range	6.9–15.1	5.2–15.8
Leukocytes, $\times 10^9$/l		
Median	57.2	78.2
Range	2.7–236	10.3–299
Lymphocytes, $\times 10^9$/l		
Median	54.8	72.9
Range	0.95–200.6	4.2–260.2
Thrombocytes, $\times 10^9$/l		
Median	133	126
Range	58–284	40–208
Abnormal LDH	7	5

One non-pretreated patient was diagnosed with both CLL and NHL-A.

Hematological Toxicities

All 22 patients were affected by some hematological toxicity of WHO grade 2 or more (table 2). Thirteen episodes of WHO grade 3 leukopenia occurred as well as two WHO grade 4 leukopenia, ten WHO grade 3 neutropenia and twenty-three WHO grade 4 neutropenia episodes. Thrombocytopenia grade 3 occurred during three courses and grade 4 during three courses.

Non-Hematological Toxicities

Twenty-two patients were evaluable for non-hematological toxicities (tables 3, 4). Alopecia, mucositis, hepatic and renal failure were not observed. Grade 1 fatigue and weight loss were present predominantly during the first two courses. Major non-hematological toxicities included pulmonary infections. Grade 2 nausea was noted during two courses in 1 patient. One patient who later developed tuberculous peritonitis had grade 3 emesis, an-

Table 2. Hematological toxicity during treatment (WHO grade ≥2)

Course No.	Patients treated	Patients with toxicity >G1	Toxicity events, n											
			hemoglobin			leukocytes			neutrophils			thrombocytes		
			G2	G3	G4	G2	G3	G4	G2	G3	G4	G2	G3	G4
1	22	16	5[1]	3[1]	1[1]	2	4	1	1	2	8	4	2	1
2	17	11	2	1	2	4	1	0	2	2	5	3	0	1
3	13	7	1	0	2	4	3	0	2	1	2	1	0	0
4	10	5	1	0	1	2	2	0	2	1	2	0	0	0
5	10	7	1	1	1	2	2	1	1	2	4	0	1	0
6	5	4	0	1	0	0	1	0	2	0	1	0	0	1
Total			10	6	7	14	13	2	10	8	22	8	3	3

G = Grade.
[1] Five pretreated patients had a hemoglobin level of 5.2–8.5 g/dl.

Table 3. Nonhematological toxicity during treatment

	Course 1 (n = 22)	Course 2 (n = 17)	Course 3 (n = 13)	Course 4 (n = 10)	Course 5 (n = 10)	Course 6 (n = 5)
Weight loss	12	7	3			
Hospitalization	4	2	3		1	
Fatigue	1 (G3)					
Myalgia		1 (G3)				
Headache	1 (G2)					
Constipation	1 (G2)					
Nausea	1 (G2)	1(G2)				
Vomiting	1 (G3)	1				
Neurological		1 (G4)				

G = Grade.

other patient suffered from grade 3 myalgia, and grade 4 radiculopathy occurred in 1 patient with herpes zoster. Fatal tuberculous peritonitis occurred in a woman aged 71 years with non-pretreated NHL who had had a primary lung infection in 1943. Pulmonary tuberculosis was found in a splenectomized CLL patient previously treated with cladribine who died few months later. Fatal *Pneumocystis carinii* lung infection developed in a CLL patient who had previously been treated with alkylating agents, prednisone and fludarabine.

Long-Term Toxicities

Grade 2 hematological toxicities as worst toxicity developed in 1 patient, grade 3 in 1 and grade 4 in 17 (tables 5, 6). Three patients did not develop any significant toxicity (grade >1) during follow-up. One of the grade 4

Table 4. Major infectious toxicity (n = 77 cycles)

Infections	Grade 2	Grade 3	Grade 4	Grade 5 (fatal)
Urine/prostate	2	1		
Herpes simplex	1			
Herpes varicella		1/1		
Lung/ear	8	2	1/1	
P. carinii				1
Tuberculosis		1		
Stomatitis	1			
Fever of unknown origin	1			
Tuberculous peritonitis				1

One patient had both herpes varicella and lung/ear infections, and another patient had lung/ear and *P. carinii* infection concomitantly.

Table 5. Worst grade of hematological complications during follow-up (n = 17 patients)

	Grade 2	Grade 3	Grade 4
All	9	6	5
Anemia	4	1	8
Thrombocytopenia	2	1	9
Neutropenia	1	1	15

Table 6. Non-hematological complications during follow-up (n = 17 patients)

Diagnosis	Complications	Grade
Pretreated CLL	cutaneous basalioma	
	Legionella pneumonia	2
	pulmonary infection (n = 5)	2
	herpes zoster	4
	herpes varicella	5 (fatal)
	pulmonary idiopathic fibrosis	
	thrombocytopenia	4
	urinary tract infection	3
Pretreated NHL	myelodysplastic syndrome and AHIA	1
	AHIA	1
	herpes zoster (n = 2)	2/3
Untreated CLL	virus-induced pericarditis	
	virus-induced AHIA	
	herpetic esophagitis	3
	pulmonary infection	2
	idiopathic thrombocytopenia	
Untreated NHL	breast cancer	

anemias was diagnosed in a patient who presented with autoimmune hemolytic anemia in relapse. One case of transient virus-induced hemolytic anemia was discovered as well as 1 case of myelodysplastic syndrome and 2 cases of grade 4 thrombocytopenia and 1 case of grade 4 neutropenia.

Sixteen non-hematological toxicities were diagnosed. Infections occurred at a mean time of 18 months after the end of trial treatment. Generalized herpes varicella infection complicated by fatal septic shock occurred 22 months after the end of treatment in a previously treated CLL patient.

Breast carcinoma was diagnosed in a patient 1 month after the end of trial treatment, and cutaneous basalioma occurred in another patient 1 year after completion of trial treatment.

Response

Twenty patients were evaluable for response. CR was observed in 7 (35%) and PR in 8 patients (40%), with an overall response rate (OR) of 75%. Non-pretreated patients had a higher response rate since 7 out of 8 responded whereas 8 out of 12 pretreated patients responded. NHL patients all responded with 3 CR and 2 PR (100%). Four out of 5 non-pretreated CLL responded (1 CR and 3 PR) whereas the 9 pretreated CLL patients had a lower response rate (3 with CR, 2 with PR and 4 patients with stable disease). In all but 2 patients responses were obtained after one or two courses. In the remaining 2 patients, responses were obtained after three and five courses, respectively.

Relapse/Progression/Survival

Thirteen patients progressed or relapsed at a median time to progression of 31 months (fig. 1). Median time to progression from the best result obtained in the 20 evaluable patients was 25 months. Median response duration for the 7 patients in CR was 9 months. Ten patients have died. Median overall survival time from trial entry was 60 months for the 22 treated patients (fig. 2).

Discussion

The CR rate obtained in the present trial was superior to those obtained with single alkylating agents or purine analogues. This is another in vivo confirmation of the additive effect that had been previously observed in vitro [14, 15]. In addition, overall response measured in our study was also comparable to already published data [16, 20–29]. Median overall survival was 5 years in a group of patients in which many had aggressive disease, e.g. a high LDH and extranodal involvement, and half of whom were heavily pretreated, some already with purine analogues, confirming the efficacy of this multidrug combination.

However, myelosuppression was severe and infections included *P. carinii*, tuberculosis mycobacteria and herpes zoster. These must be considered as major serious adverse reactions. Three of the 10 deaths were directly related to infections, confirming the profound and prolonged immunosuppressive effect of cladribine [5]. Several factors may have contributed to this high rate of late complications. First, due to the prolonged decrease in CD4 lymphocyte and monocyte counts, patients are at increased risk of infections for a long period of time [30]. Second, three quarters of the patients presented with CLL, and

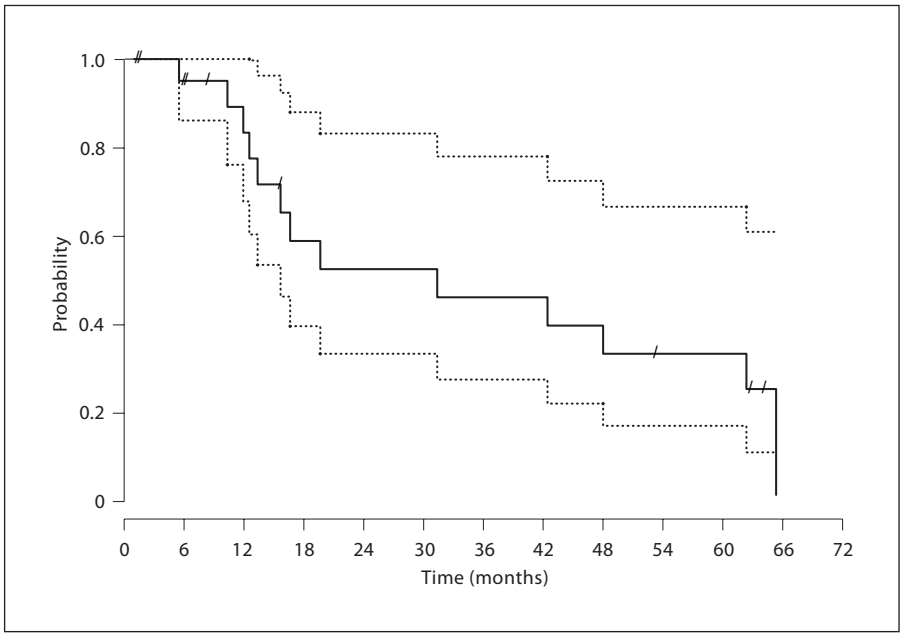

Fig. 1. Time to progression or relaxpse (with 95% confidence intervals).

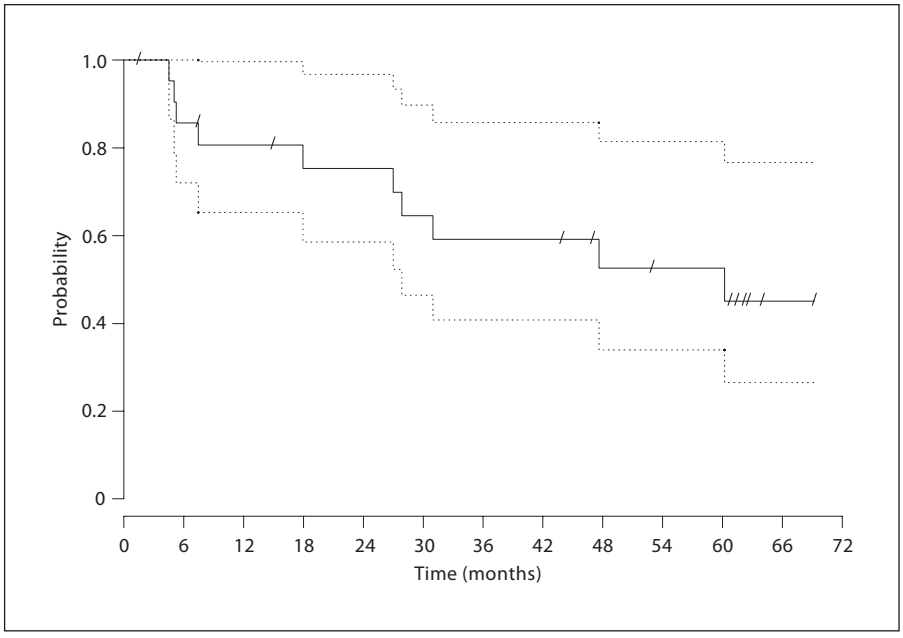

Fig. 2. Overall survival (with 95% confidence intervals).

this disease carries per se a high risk of infectious morbidity and mortality [31]. Third, cytotoxic chemotherapy, corticosteroids and purine analogues are all known to increase the incidence and severity of opportunistic infections [32]. Fourth, routine antimicrobial prophylaxis was not recommended in the original study protocol and this may have exposed patients at increased risk of infections. Thus, the supplementation of prednisone to cyclophosphamide and cladribine may be responsible for these complications, especially in pretreated patients who were not administered antimicrobial prophylaxis according to the study protocol.

Cladribine produces little if any extramedullary toxicities, but therapy-related myelodysplastic syndrome and secondary malignancies have been reported in the literature [33, 34]. In the present trial, breast cancer and basal cell skin carcinoma were diagnosed during the follow-up (1 month and 1 year after the end of the treatment,

respectively). However, the prevalence of both disorders in the general population and the short interval from the treatment allow us to consider these events more as a coincidence rather than an additional toxic effect of cyclophosphamide and cladribine.

During the follow-up, 2 patients developed thrombocytopenia and 2 others developed autoimmune hemolytic anemia (AIHA), a known complication of CLL also described as a complication of cladribine treatment [35]. It is difficult to draw a definite conclusion regarding the causal relationship of either the disease or the treatment and the incidence of AIHA since some patients had AIHA already before treatment and 1 presented with AIHA during relapse.

In conclusion, the optimal therapy for NHL-A and CLL patients is the subject of continued investigation, but it may now be positively influenced by new agents such as purine analogues. The combination of cladribine, cyclophosphamide and prednisone appears very efficacious but far too toxic in previously treated patients. In addition, the association of cladribine with corticosteroids must probably be abandoned.

Nowadays, humanized monoclonal anti-B-lymphocyte antibodies have a greater role to play in the treatment of CD20+ lymphoid malignancies. Encouraging results have already been obtained with the combination of cladribine and rituximab [36]. On the other hand, interesting data have also been reported with the combination of cyclophosphamide, rituximab and another purine analogue, fludarabine [37, 38]. A direct comparison between both purine analogues remains thus to be done.

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