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Original Paper

The Effect of 2-h Infusion of 2-Chlorodeoxyadenosine (Cladribine) with Prednisone in Previously Untreated B-cell Chronic Lymphocytic Leukaemia

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2-Chlorodeoxyadenosine (2-CdA) is a new antimetabolite chemotherapeutic agent active in indolent lymphoid malignancies. In this retrospective study, 69 previously untreated patients with B-cell chronic lymphocytic leukaemia (B-CLL) were treated with 2-CdA administered at a dose of 0.12 mg/kg daily in 2-h intravenous infusion for 5 consecutive days. 45 patients also received prednisone 30 mg/m^2 orally each day for 5 days starting with 2-CdA courses. Patients were given 2–6 courses (mean 4.6) of 2-CdA repeated usually at monthly intervals. If a complete response was achieved, no further 2-CdA courses were administered. Guidelines for response were those developed by the NCI Sponsored Working Group. Complete response (CR) was achieved in 26 (38%) and partial response (PR) in 27 (39%) cases, giving an overall response rate of 77%. 16 patients (23%) did not respond to 2-CdA. In the subgroup of 45 patients receiving 2-CdA with prednisone, CR was obtained in 15 (33%) and PR in 20 (44%) patients giving an overall response rate of 78%. CR was achieved in 11 (46%) out of 24 patients treated only with 2-CdA and in 7 cases (29%) PR was observed, giving an objective response rate of 75%. The differences between both subgroups were not statistically significant. However, we observed a relationship between the response and the number of courses of 2-CdA given in patients receiving and those not receiving prednisone. In the subgroup receiving 2-CdA with prednisone, an earlier response to 2-CdA was observed. In this group a response was achieved in 9 (20%) patients after two courses of 2-CdA and in 18 (40%) after four courses. In the subgroup receiving only 2-CdA, 17 (71%) responses were obtained after six cycles. © **1997 Elsevier Science Ltd.**

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INTRODUCTION

2-CHLORODEOXYADENOSINE (2-CdA), a new purine analogue, has been synthesised by Carson and associates [1] and Kazimierczuk and associates [2] by simple substitution of a chlorine atom for a hydrogen atom at position 2 of the purine ring. It is phosphorylated by deoxycytidine kinase and accumulates as chlorodeoxyadenosine triphosphate (2-CdATP) [3]. High activity of this enzyme in lymphocytes along with low 5-nucleotidase activity probably explains its relatively high selectivity for these cells [4–7].

2-CdA has been found to be quite effective in the treatment of patients with chronic lymphocytic leukaemia (CLL),

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even when they prove resistant to other therapies [8–10]. In a study reported by Saven and associates [11] on 90 patients with CLL previously treated with other regimens, an overall response rate of 44%, including 4% complete response (CR), was achieved after an average of two courses of 2-CdA, given as a 24-h infusion for 7 days. In our previous study we observed similar results with the treatment of refractory CLL patients with 2-h infusion of 2-CdA [10]. CR was achieved in 5 (5.4%) out of 92 previously treated patients and partial response (PR) in 28 (30.4%) cases. A higher response rate in small groups of patients was recorded in previously untreated CLL patients, after treatment with 2-CdA in 24-h [12] as well as 2-h [13] intravenous infusions. In the studies reported so far 2-CdA was given without corticosteroids both in previously treated and in untreated patients.

In this retrospective study, we present the results of B-CLL treatment with 2-CdA administered in 2-h intravenous infusions for 5 consecutive days and have analysed the influence of prednisone on the response to cladribine.

PATIENTS AND METHODS

Patients

We retrospectively analysed a group of 69 previously untreated patients with progressive or symptomatic B-CLL who were treated with 2-CdA. 45 of them received additionally prednisone. The characteristics of the patients are presented in Table 1.

All the patients fulfilled the National Cancer Institute-Sponsored Working Group diagnostic criteria for CLL [14]. Pretreatment evaluation included medical history, physical examination, complete blood cell count, differentiation analysis, chemical survey, bone marrow examination and serum immunoglobulin level quantitation. The patients had documentation of lymphocytosis with the absolute lymphocyte count greater than 10×10^9/l and had more than 30% lymphocytes in the bone marrow. Cell markers studies were performed to confirm B-cell origin and monoclonal proliferation, including immunoglobulin heavy- and light-chain, CD3, CD5, CD10, CD19, CD23 and FMC-7. We used monoclonal antibodies manufactured by DAKO, Denmark and two-colour flow cytometer (Coulter, U.S.A.).

The clinical stage of disease was determined at the time of initiation of 2-CdA according to the Rai classification [15]. The distribution is shown in Table 1.

The patients included in the study were required to be over 18 years of age. At the start of therapy, they had normal renal (creatinine < 1.0 mg%) and hepatic (bilirubin < 1.0 mg%) functions and were free of active infection. Autoimmune haemolytic anaemia (AIHA) was diagnosed with Coomb's positive test in 1 patient.

The study was approved by the Local Ethical Committee and the patients had signed the consent form.

Treatment modality

2-Chlorodeoxyadenosine was supplied by the Foundation for the Development of Diagnostics and Therapy, Warsaw, Poland, and was synthesised according to the method of Kazimierczuk and associates [2]. 2-CdA was administered at a dose of 0.12 mg/kg daily by 2-h intravenous infusions for 5 consecutive days. 45 patients received prednisone 30 mg/m^2 orally each day for 5 days starting with 2-CdA courses.

Patients were given 2–6 courses (mean 4.6), repeated usually at monthly intervals. If a complete response was achieved, no further 2-CdA treatment was administered. If severe infections or progressive cytopenia developed (thrombocytopenia $< 50.0 \times 10^9$/l and neutropenia $< 1.0 \times 10^9$/l), 2-CdA therapy was stopped until the haematological parameters increased. The drug was then readministered. In such cases, time intervals between 2-CdA cycles were longer than one month, ranging from 2 to 4 months.

Packed red blood cells were transfused for symptomatic anaemia or prophylactically if the haemoglobin level was lower than 7.0 g/dl. Platelets were administered prophylactically if the platelet count was less than 15.0×10^9/l. In order to prevent hyperuricaemia, allopurinol (300 mg daily) was routinely given. No patients received antibiotics prophylactically.

Response criteria

Physical examination and peripheral blood analysis were performed before inclusion in the study and after every 2-CdA course, and the response to the drug was estimated.

Table 1. *Clinical characteristics of B-CLL patients before treatment*

		Mode of treatment	
	All patients	2-CdA with prednisone	2-CdA alone
Number of patients	69	45	24
Age (in years, mean ± SD)	59 ± 11	59 ± 12	54 ± 11
Sex			
M	23 (33)	19 (42%)	4 (17%)
F	46 (67%)	26 (58%)	20 (83%)
Rai stage			
0	4 (6%)	4 (9%)	0
I	10 (15%)	7 (16%)	3 (13%)
II	23 (33%)	13 (29%)	10 (42%)
III	13 (19%)	9 (20%)	4 (17%)
IV	19 (28%)	12 (27%)	7 (29%)
Mean Hb concentration (g/dl)	10.5	11.4	10.1
Mean number of white blood cells ($\times 10^9$/l)	106.8	103.6	112.8
Mean number of platelets ($\times 10^9$/l)	138.8	143.7	129.5
Mean number of 2-CdA courses	4.6	4.2	5.3
Mean time of observation from diagnosis (in months)	28.2	22.0	40.5
Mean time from the start of 2-CdA (in months)	4.5	4.4	4.7

Bone marrow aspiration and immunophenotypic studies were performed to confirm complete remission.

Guidelines for response were those developed by the NCI-Sponsored Working Group [14]. Complete response (CR) required the absence of symptoms and organomegaly, a normal complete blood cell count (absolute neutrophil count $>1.5 \times 10^9$/l, haemoglobin concentration >11.0 g/dl, platelet count $>100.0 \times 10^9$/l), and bone marrow with less than 30% of lymphocytes for at least 2 months. Partial response (PR) was considered a 50% or greater decrease in the size of lymph nodes, liver and spleen, and peripheral blood findings either identical to those of CR or improved over pretherapy values by at least 50%. No bone marrow evaluation was required for determination of PR. All other responses were evaluated as no response. Clinical relapse was defined according to Robertson and associates [16] as an increase in the absolute lymphocyte count above 10.0×10^9/l, more than 50% lymphocytes on marrow differential analysis, more than 50% increase in the sum of the sizes of at least two lymph nodes, appearance of new lymph nodes, more than a 50% increase in the liver or spleen below the costal margin, new appearance of palpable hepatosplenomegaly or development of an aggressive lymphoma.

Toxicity monitoring

Haematological toxicity was evaluated according to the criteria developed by the NCI-Sponsored Working Group [14]. All other toxic effects were monitored and assessed according to the Eastern Cooperative Oncology Group criteria [17].

The blood counts, creatinine, bilirubin, GOT, GPT, ECG, urine analysis and general physical examination were serially evaluated and recorded.

Statistical analysis

Statistical analysis of the difference in percentages of patient responses was evaluated by chi-square test at the level of confidence $P < 0.05$.

RESULTS

The results of the treatment of patients with B-CLL using 2-CdA are summarised in Table 2. The criteria for CR were fulfilled in 26 (38%) and PR in 27 (39%) patients giving an overall response rate of 77%. 16 patients (23%) did not respond to 2-CdA. In the group of 45 patients receiving 2-CdA with prednisone, response was achieved in 35 (78%; 15 CR and 20 PR patients). One patient with Coomb's positive autoimmunohaemolytic anaemia benefited from the treatment of 2-CdA in combination with prednisone, which resulted in complete resolution of haemolysis. He entered PR after six courses. 24 patients were treated only with 2-CdA and 18 (75%) responded to such therapy (11 CRs and 7 PRs). The results in both subgroups are similar and the differences were not significant statistically ($P > 0.05$), which indicates that oral steroids added to 2-CdA do not improve the response rate (CR + PR) in B-CLL patients.

Table 2. Results of the treatment of B-CLL patients with 2-CdA

Response	Number of patients (percentage)		
	All patients ($n = 69$)	2-CdA and prednisone ($n = 45$)	2-CdA alone ($n = 24$)
CR	26 (38%)	15 (33%)	11 (46%)
PR	27 (39%)	20 (44%)	7 (29%)
NR	16 (23%)	10 (22%)	6 (25%)

CR, complete response; PR, partial response; NR, no response.

Table 3. The relationship between the number of 2-CdA cycles and the response (CR + PR) obtained in B-CLL patients treated with 2-CdA alone or in combination with prednisone

Mode of treatment	Number of 2-CdA cycles		
	2	4	6
2-CdA with prednisone ($n = 45$)	9 (20%)	18 (40%)	8 (18%)
2-CdA alone ($n = 24$)	0	1 (4%)	17 (71%)

However, we observed a significant difference between response and the number of courses of 2-CdA in patients receiving or not receiving prednisone ($P < 0.05$; Table 3). In 45 patients receiving 2-CdA and prednisone, response was achieved after two courses of 2-CdA in 9 (20.0%) and after four courses in 18 (40.0%) cases. In the group of 24 patients who were given only 2-CdA, only 1 entered PR after four cycles, and the other 17 (71%) responses were obtained after six cycles of 2-CdA.

The adverse reactions after 2-CdA given with or without steroids are summarised in Table 4. The most frequent toxic effects were pulmonary infections or fever of unknown origin and thrombocytopenia. Infection complications occurred in 10 (42%) out of 24 patients who did not receive prednisone, while in the group of 45 patients receiving 2-CdA with prednisone, adverse reactions were noticed in 17 (38%) patients. It may suggest that addition of such an immunosuppressive agent as prednisone to 2-CdA does not enhance the susceptibility of B-CLL patients to infections.

We also observed neutropenia occurring more frequently in patients who did not receive steroids, but the number of cases was too small to draw any conclusion.

6 patients in III and IV Rai stage died 4–7 months (mean 5.4 months) from the start of 2-CdA. 3 had received two cycles and 2 had received three courses of the drug, but none responded to the therapy. 2 patients who were given 2-CdA and prednisone died of haemorrhage in the central nervous system caused by drug-induced thrombocytopenia. Infectious complications were the cause of death in another 3 patients, 2 of whom died in septic shock and 1 because of severe bilateral pneumonia. In 1 patient we observed allergic dermatitis followed by marked eosinophilia in peripheral blood (absolute eosinophil count 1.6×10^9/l) which occurred after four cycles of 2-CdA given in combination with prednisone. He partially

Table 4. Side-effects of 2-CdA in 69 B-CLL patients

Side-effect	Number of patients	
	2-CdA with prednisone	2-CdA alone
Thrombocytopenia $< 50 \times 10^9$/l	2	3
Neutropenia $< 1.0 \times 10^9$/l	2	—
Infections and fever of unknown origin	7	10
Allergic dermatitis with eosinophilia	1	—
Increase in aminotransferase levels	1	—
LDH increased	—	1
Creatinine increased	1	—
None	32	10

responded to the treatment, but this effect was transient and he died because of disease progression.

DISCUSSION

The effectiveness of 2-CdA has been established in the treatment of B-cell indolent lymphomas, but the results obtained by various authors are different and depend mainly on patient selection and response criteria. In patients with advanced, progressive or relapsed B-CLL as well as in B-CLL resistant to an alkylating agent, the reported overall response rate to 2-CdA ranges from 22% to 52% [8, 11, 18, 19]. In all these studies 2-CdA was administered in continuous 24-h intravenous infusion for 5 or 7 consecutive days at a dose of 0.1 mg/kg/d. Juliusson and Liliemark [9] reported a high overall response rate of 67% in 18 patients with previously treated B-CLL who were given 2-CdA at a 2-h intravenous bolus for 5 consecutive days at a dose of 0.1 mg/kg daily, and confirmed this result in a larger group of patients [20]. Similar results were reported by Delannoy and associates [13] and Robak and associates [10]. In the present study, an overall response rate in the group of 69 untreated patients was 77%, which confirms a significantly higher effectiveness of 2-CdA given to previously untreated in comparison with treated B-CLL patients.

In previous studies 2-CdA has been used as a single agent. Although glucocorticosteroids have been shown to exert an antileukaemic effect in CLL, their application in the treatment of CLL as well as their role in combined chemotherapy have not been unequivocally established [21]. Nevertheless, the combination of prednisone with an alkylating agent, i.e. chlorambucil, resulted in a better response rate compared to either drug alone according to Han and associates [22]. For years prednisone has been given orally to B-CLL patients in combination with cytostatics, especially with alkylating drugs, but its role has not been clearly determined [22–24]. Moreover, a higher risk of infections in CLL patients treated with chlorambucil and prednisone should be taken into account, particularly in elderly patients [24]. Prednisone alone, apart from its lymphocytolytic effect, is not sufficient to induce remission in CLL and its antitumour activity in this disease is weak. For this reason glucocorticosteroids are not used as a single agent in therapy of CLL, but they are particularly applicable in immune events which complicate CLL, such as autoimmune haemolytic anaemia or immune thrombocytopenia [21, 23].

The introduction of purine analogues to the therapy of CLL has given rise to the question of whether or not steroids might increase the response rate and how such a combined therapeutic schedule might influence drug-related toxic effects. O'Brien and associates [25] did not confirm the synergistic antilymphocytic effect of fludarabine combined with prednisone in 264 patients with untreated CLL achieving response (CR + PR) in 79%. A similar conclusion may be drawn from the study of Robertson and associates [16] who treated 159 patients with fludarabine and prednisone (30 mg/m^2 daily) for 5 days and achieved a response rate of 60%. Our study seems to confirm that the addition of steroids did not influence the response to 2-CdA and the overall response rates in the two subgroups (one treated with 2-CdA alone and the other in combination with prednisone) were 75% and 78%, respectively. However, the number of patients is too small and the study is not randomised so our results must be interpreted with caution.

Unlike hairy cell leukaemia, in which a single cycle of 2-CdA may induce long-lasting, unmaintained CR [26, 27], CLL patients require repeated courses of this drug. In our study we monitored the response to 2-CdA after 2, 4 and 6 cycles of treatment. In the subgroup of patients receiving prednisone the response to 2-CdA occurred earlier than in the subgroup treated with 2-CdA alone. It may be explained by a synergistic antileukaemic effect of steroids, but the significance of this observation is not clear and a randomised trial on larger groups and longer clinical follow-up are needed to establish whether this relationship is of importance. Pharmacokinetic studies of 2-CdA made by Liliemark and Juliusson [28] revealed very similar bioavailability of the drug given intravenously or subcutaneously. Undoubtedly, the latter route of its administration is more comfortable and should be recommended especially to out-patients requiring prolonged treatment [28].

Myelosuppression and immunosuppression are major toxic effects of purine analogues given to patients with lymphoproliferative disorders [4, 9, 13, 29]. Fludarabine and 2-CdA exhibit usually mild or moderate myelotoxicity but the frequency of these drug-related complications increases in patients pretreated with an alkylating agent or polychemotherapy because of cumulative myelotoxicity [9, 25]. Myelosuppression results mainly in profound and/or prolonged neutropenia and thrombocytopenia [9, 29]. In our study, the latter were noted in a relatively small number of patients. It should be kept in mind that our patients had not been pretreated and 2-CdA was a first-line therapy so they probably had a better marrow reserve. In the analysed group of patients, we observed relatively frequent infections and fever of unknown origin after 2-CdA given alone or in combination with prednisone. However, the addition of prednisone in itself did not increase the incidence of infections, which may be explained by the fact that prednisone was given to our patients for 5 days. Such a discontinuous mode of steroid administration for a relatively short period of time probably does not lead to significant immunosuppression. It seems that prednisone does not deepen the suppressive effect of 2-CdA on the immune mechanism in CLL patients, but further randomised studies are mandatory to elucidate the problem. However, it should be noted that cladribine-induced myelosuppression and immunosuppression may have a fatal outcome and the drug must be administered with caution. The risk of death is particularly high in non-responding patients in advanced Rai stage who have unfavourable prognostic factors.

Allergic skin lesions are rarely seen in patients treated with 2-CdA. We observed them in 1 patient with CLL, with marked eosinophilia in peripheral blood. He died because of progression of CLL. In 1 patient who was splenectomised for hairy cell leukaemia, profound and prolonged eosinophilia after one course of 2-CdA was followed by long-lasting unmaintained complete remission lasting 6 years [30]. The clinical significance of eosinophilia in patients with lymphoproliferative disorders treated with 2-CdA is therefore uncertain.

Our observation does not confirm the suggestion made by Anaisse and associates [31], O'Brien and associates [25] and Saven and associates [13] that the addition of prednisone to purine analogues increases the susceptibility of patients to opportunistic infection. However, purine analogues are potent immunosuppressive agents exhibiting their lymphocytotoxic activity especially against T4 cells and this effect

persists, even for as long as 24 months after the cessation of treatment [9, 27, 29, 32].

Although the mean time of our observation was short, durable CRs from 2-CdA in advanced CLL have been reported [20]. Determination of the effectiveness of 2-CdA alone or in combination with steroids in the treatment of CLL patients will require a randomised study on a larger group of patients and a longer clinical follow-up so that the overall survival rate rather than response rate can be determined.

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