



Weekly administration of 2-chlorodeoxyadenosine in patients with hairy-cell leukemia is effective and reduces infectious complications

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Abstract

Background and Objective. It has been widely demonstrated that one single 7-day course continuous infusion (c.i.) 2-chlorodeoxyadenosine (2-CdA) at a dose of 0.1 mg/kg daily is dramatically effective in inducing high and prolonged complete remission (CR) rates in patients with hairy-cell leukemia (HCL). However, 2-CdA administration often results in severe neutropenia and lymphocytopenia both responsible for the infectious complications observed in these patients. We previously reported preliminary data regarding the effectiveness and toxicity of a modified protocol of 2-CdA administration (0.15 mg/kg 2 hours infusion once a week for 6 courses) in 25 HCL patients. This treatment schedule produced a similar overall response rate compared to standard 2-CdA regimen and appeared to be followed by a lower incidence of infectious episodes. In the present study we report response rate and toxicity of weekly 2CdA administration in a larger cohort of patients and with a longer follow-up.

Design and Methods. In a group of HCL patients with a pronounced decrease in neutrophils count ($< 1 \times 10^9/L$), we modified the standard protocol (0.1 mg/kg daily \times 7 days c.i.) by administering 2-CdA at a dose of 0.15 mg/kg 2 hours infusion once a week for 6 courses. Thirty HCL patients, 24 males and 6 females with a median age of 56 years (range 37-76), entered into this protocol. Seventeen out of 30 patients were at diagnosis while the remaining 13 had been previously treated with α -interferon (α -IFN) (7), or 2-CdA (4) or deoxycoformycin (DCF) (2).

Results. Overall, 22/30 (73%) patients achieved CR and 8 (27%) partial remission (PR) with a median duration of response at the time of writing of 35 months, ranging from 6 to 58 months. Five patients (1 CR and 4 PR) have so far progressed. The treatment was very well tolerated. Five out of 30 patients (16%) developed severe neutropenia (neutrophils $< 0.5 \times 10^9/L$) and only in two of them we did register an infectious complication which required treatment with systemic antibiotics and granulocyte colony-stimulating factor (G-CSF).

Interpretation and Conclusions. In conclusion, we confirm that weekly administration of 2-CdA at a dose of 0.15 mg/kg for 6 courses appears to be very effective in HCL inducing a high CR rate, similar to that observed with daily c.i. administration. CR durability and relapse/progression rates are also comparable to standard 2-CdA schedule. Moreover this new regimen seems to be safer in pancytopenic patients, markedly reducing life-threatening infectious complications.

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Key words: HCL, 2-CdA, CR, infectious complications

The treatment options for hairy cell leukemia (HCL) have increased in these last 10-15 years and currently HCL patients can benefit from several agents such α -interferon (α -IFN), deoxycoformycin (DCF) and 2-chlorodeoxyadenosine (2-CdA). Although complete remission rates may differ from 5-10% with α -IFN¹⁻³ to 60-80% with DCF^{4,5} and 2-CdA,⁶⁻⁸ the prognosis has improved dramatically with 80-90% of patients surviving at least 10 years with any of these treatments. Given these considerable results, it is extremely important in HCL patients to reduce any risk of toxic deaths possibly related to severe infections, more frequently observed after treatment with DCF and 2-CdA.⁹⁻¹¹ In fact, it was observed that this latter agent frequently induces severe neutropenia and CD4⁺ lymphocytopenia,¹²⁻¹⁵ probably responsible for fever and/or infectious complications in a relevant number of treated patients. Subsequently, attempts to reduce the incidence of infectious complications by decreasing the dose of 2-CdA have been made by several authors including us.¹⁶⁻¹⁸ In fact in a previous preliminary report we showed, in a selected group of HCL patients with pronounced impairment of peripheral blood values, that weekly administration of 2-CdA was as effective as daily administration with a concomitant reduction of febrile episodes and infectious complications.¹⁷ The present study confirms and extends, in a larger number of patients and with a longer follow-up, the encouraging previous results on the effectiveness and mild toxicity of weekly 2-CdA in HCL patients.

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Design and Methods

Thirty bone marrow biopsy proven HCL patients at diagnosis or in progression after previous therapies, showing a pronounced decrease in peripheral blood values (neutrophils $<10^9/L$, platelets $<50 \times 10^9/L$), were enrolled into this study. Twenty-four were males and 6 females with a median age of 56 years (range 37-76), and all were evaluable for clinical response (Table 1).

2-CdA (kindly provided by Janssen-Cilag, Italy) was administered to each patient at a dose of 0.15 mg/kg once a week for 6 weeks after having given informed consent. Patients were given antibiotic prophylaxis with ciprofloxacin for the first 2 weeks of 2-CdA therapy. Complete blood counts with differentials and chemistry panels were performed weekly during the administration of 2-CdA. Subsequently, patients were monitored for the same parameters monthly for 6 months. Bone marrow biopsies were carried out before therapy and 2 and 6 months after therapy, and thereafter every 6 months. Samples were decalcified, embedded in paraffin and sections were prepared for routine histology (hematoxylin-eosin, Giemsa and Gomori) and for immunohistochemical studies with specific monoclonal antibodies such as DBA44, CD45RA and CD20, as previously described.⁸

Criteria for response were defined according to the consensus resolution, as previously described.¹⁹ Briefly, complete remission (CR) was defined as the disappearance of hairy cells (Hc) from bone marrow and peripheral blood together with the regression of splenomegaly and a complete recovery of peripheral blood counts (Hb >12 g/dL, platelets $>100 \times 10^9/L$, neutrophils $>1.5 \times 10^9/L$). Additional requirements for CR in our analysis were no Hc in bone marrow biopsies observed by routine histology and $<1\%$ Hc by immunostaining. Partial response (PR) was characterized by normalization of peripheral blood counts and a decrease in bone marrow infiltration of at least 50%.

Table 1. Patients' characteristics, clinical outcome and toxicity with respect to previous treatment.

	Total	Untreated	Previously treated		
			α -IFN	DCF	2-CdA
N° of patients	30	17	7	2	4
Median age	56	-	-	-	-
Sex (M/F)	24/6	-	-	-	-
Complete remission	22/30	13/17	5/7	2/2	2/4
Partial remission	8/30	4/17	2/7	0/2	2/4
Severe neutropenia	5/30	3/17	1/7	0/2	1/4
Infectious episodes	2/30	2/17	0/7	0/2	0/4

Results

All 30 HCL patients were fully evaluable for clinical and hematologic response. Seventeen out of 30 patients were at diagnosis while the remaining 13 had been previously treated with α -IFN (7 cases), 2-CdA (4 cases) and DCF (2 cases). In these latter 6 patients previously treated with nucleoside derivatives, the interval between the two treatments was 12, 18, 24, 36, 30 and 48 months, respectively. Overall, 22/30 (73%) patients achieved CR and the remaining 8 (27%) achieved a PR. The median duration of response was 35 months, ranging from 6 to 58 months. All CRs were documented by routine histology and by immunohistochemical studies. Table 1 illustrates patients' characteristics, clinical outcome and toxicities according to previous treatments. The majority (5/6) of untreated patients with less than 50% Hc bone marrow infiltration at diagnosis, achieved a CR (data not shown). In addition, it is worth noting that both patients who had been previously treated with DCF and 2/4 patients who had progressed after treatment with 2-CdA at a dose of 0.1 mg/kg/day c.i. for 7 days, achieved CR. The time to achieve a response was similar to that observed with daily 2-CdA and in responsive patients Hc were yet undetectable in the bone marrow 2 months after the end of therapy. In 2 patients CR was first documented about 6 months after the last weekly course of therapy. So far, the disease has progressed in only 5/30 (17%) patients: in one of the complete responders and 4 of the partial responders with the progression occurring after 14 months in the complete responder and after 9, 10, 11 and 18 months, in the partial responders. However, only 3 of the patients in progression needed to be retreated, all with α -IFN at a conventional dose of 3 MU 3 times a week. All patients are so far alive.

Overall the treatment was very well tolerated and it is noteworthy that only 5/30 patients (16%) developed severe neutropenia (neutrophils $<0.5 \times 10^9/L$). Infectious episodes due to Gram-positive germs requiring the use of systemic antibiotics and G-CSF were documented in only 2 of these neutropenic patients. No fungal infections were recorded. Only one patient developed a febrile episode ($<38^\circ C$) which lasted 24 hours. Therefore, only 7% (2/30) of the patients treated with this protocol suffered from infectious complications, this being an evident reduction of toxicity with respect to other conventional studies including our historical control group (Table 2).

Discussion

The present study confirms in a larger number of cases and with a longer follow-up that weekly administration of 2-CdA in HCL patients at a dose of 0.15 mg/kg for 6 weeks is effective as standard protocols in inducing high CR rates and safer in term of infectious complications. Moreover, CRs appear to be durable and recurrence of disease is similar to that observed

Table 2. Incidence of documented infectious complications and/or febrile episodes requiring hospitalization recorded in this study and in other published reports.

	N° episodes/ N° patients	Treatment schedule	χ^2 -test
Lauria et al. (1997)	9/40	daily	NS
Talman et al. (1997)	12/26	daily	$p < 0.01$
Juliusson et al. (1995)	47/94	daily	$p < 0.01$
Lauria et al. (present data)	2/30	weekly	

after a conventional treatment schedule.^{16, 20, 21}

The use of α -IFN first, and more recently of DCF and 2-CdA purine analogs, has dramatically improved the clinical course and prognosis of HCL patients, allowing high CR rates ranging from 60 to 80% as reported in several studies.⁵⁻⁸ Like DCF, 2-CdA either administered as a c.i. or as a 2-hour infusion, can frequently induce severe neutropenia, often responsible for life-threatening infectious complications within two weeks by the end of therapy. In particular, infections due to Gram-positive bacteria, candida, and viruses have been reported.^{11, 15}

In order to limit the incidence of long-lasting febrile episodes and documented infectious episodes, Juliusson *et al.*¹⁶ treated a group of HCL patients with a significantly reduced daily dose of 2-CdA. Despite a lower dose of the drug, the authors recorded a CR rate similar to that observed with standard regimens of 2-CdA. However, they did not also obtain a significant reduction in the number and severity of infectious episodes. Taking into account these results, our attempt to limit the toxic complications of 2-CdA was based on the hypothesis that delayed intervals between drug infusions could still be effective on an indolent disorder such as HCL but could result in reduced myelotoxicity and infections related to severe hematologic impairment. A similar approach was previously successfully attempted with DCF; discontinuation of this agent every two weeks resulted in fewer toxic side effects without affecting the CR rate.²²

We first reported preliminary data on 25 severely neutropenic HCL patients treated with weekly administrations of 2-CdA at full dose for six weeks.¹⁷ In that previous study CRs (76%) and overall response (100%) rates were very satisfying and comparable to those reported by other authors employing 2-CdA following a conventional schedule. Moreover, treatment-related toxicity and in particular infectious complications appeared to be reduced. Two major issues had still to be addressed: 1) could weekly administration of 2-CdA adversely affect durability of the response? and 2) would this reduction in infectious complications be confirmed in a larger group of patients? Thus in the present study we reported the

efficacy and toxicity of weekly 2-CdA in a larger cohort of patients with a more adequate follow-up. By comparing the results obtained using this new schedule with those from standard 2-CdA regimens previously reported in the literature and also with those utilized in our center, we confirmed that weekly administration of 2-CdA is as effective as both c.i. or 2-hour i.v. daily administration in terms of CR and progression rates. In fact we observed an overall response rate of 100% with a CR rate of 73%. Weekly administration of 2-CdA did not appear to affect the durability of response since, with a median follow up of 35 months, the disease has progressed in only 5/30 patients (17%) so far. The time to obtain a clinical response was similar to that observed with daily 2-CdA, and in only two cases was CR documented 6 months after the end of the treatment. Also, both patients who had relapsed after treatment with DCF and 2/4 patients who had relapsed after 2-CdA achieved a new CR, suggesting that sensitivity to purine analogs may not be lost during relapse, and that re-treatment with 2-CdA is frequently effective in HCL patients, as previously reported.¹⁹

We also confirmed that toxic side effects with this regimen were negligible. In fact we observed less severe and persistent neutropenia and the incidence of infectious-related complications was significantly reduced since only 2 of 30 (7%) patients experienced severe infectious episodes requiring hospitalization and treatment with systemic antibiotics and G-CSF. These findings are particularly important taking into account that almost all patients started the treatment with less than $1 \times 10^9/L$ neutrophils. Furthermore, it should be emphasized that no infections were recorded even in those patients who had been previously treated with DCF or with 2-CdA. The role of prophylactic antibiotic treatment in reducing infectious complications was probably minimal since the treatment was brief (only for the first two weeks) and the same prophylaxis had not been associated with such good results in our historical group. Thus the weekly approach allowed us to treat a group of patients at high risk, because of severe neutropenia, safely without decreasing the dose of the drug, and without inducing life-threatening hematologic toxicity.

In conclusion, these data strongly suggest that weekly administration of 2-CdA is very effective and probably safer than standard 2-CdA daily regimens. It could, therefore, be preferred as treatment of choice in HCL patients showing more pronounced cytopenia at the time of treatment.

Contributions and Acknowledgments

FL was the principal investigator, and was responsible for the conception of the study, its design, direct supervision and critical revising of the final version of the manuscript. MB contributed to data handling and interpretation and wrote the paper. GM and DRa collaborated in the design of the study, data handling and interpretation. PLZ and DRo were

involved in recruitment and day-to-day contact with patients. All the authors gave their critical contribution to the manuscript and approved its final version.

Disclosures

Conflict of interest: none.

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