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Long-term follow-up of hairy cell leukemia patients treated with 2-chlorodeoxyadenosine

PIER LUIGI ZINZANI, MASSIMO MAGAGNOLI, MAURIZIO BENDANDI, MONICA TANI, VITTORIO STEFONI, CLAUDIA CELLINI, SIMONETTA POGGI, MILENA PICCIOLI, STEFANO PILERI, SANTE TURA
Institute of Hematology and Medical Oncology "Seràgnoli", University of Bologna, Italy

ABSTRACT

Background and Objectives. **The management of patients with hairy cell leukemia (HCL) has evolved significantly over the past two decades. In fact, both 2'-deoxycoformycin (DCF) and 2-chlorodeoxyadenosine (2-CdA) induce complete response (CR) in the majority of the patients with HCL. However, fewer data exist on the long-term follow-up of patients who have undergone the characteristically brief exposure to 2-CdA therapy. Thus, it is important to evaluate such long-term outcome data in order to increase understanding of the efficacy of this agent in the management of HCL.**

Design and Methods. **We reviewed the long-term follow-up data of 23 HCL patients pretreated with α-interferon and then treated with 2-CdA administered as a single continuous IV infusion for 7 days at the dose of 0.1 mg/kg/day in our institute between January 1991 and February 1992.**

Results. **Of 23 patients, 19 (83%) achieved a CR and 4 (17%) a partial response (PR), with an overall response rate of 100%. After a median follow-up of 102 months (range: 96-108), there have been 9 (39%) relapses. In the PR subset 100% of patients relapsed within the first 45 months of follow-up. In the group of patients who obtained a CR, 26% relapsed; all these relapses occurred between 54 and 86 months. Overall, the median time to relapse was 54 months (range: 16-86). All relapsed patients were re-treated with 2-CdA at the dose of 0.15 mg/kg/day for 5 days in a 2-hour infusion, and 67% and 22% then obtained CR or PR, respectively. The median duration of this second response was 48 months (range: 22-80). All but one of these patients still maintain the second response to 2-CdA. The 9-year overall and the relapse-free survivals are 91% and 70%, respectively.**

Interpretation and Conclusions. **In HCL patients a single dose of 2-CdA induces a long-term CR with a 9-year survival > 90%. Over 50% of patients appear to be clinically cured by this procedure, but the lack of a long-term plateau in the relapse-free survival curve means caution on this point is still warranted.**

Key words: HCL, 2-CdA, 9-year follow-up, re-treated patients

Correspondence: Pier Luigi Zinzani, M.D., Istituto di Ematologia e Oncologia Medica "Seràgnoli", Policlinico S.Orsola, Via Massarenti 9, 40138 Bologna, Italy. Phone: international +39-051-390413 – Fax: international +39-051-398973 – E-mail: plzinzo@med.unibo.it

Over the past decades several agents have completely modified therapeutic approaches to hairy cell leukemia (HCL) and the prognosis of this disease. First of all, α-interferon (α-IFN) has repeatedly shown a clear beneficial effect in most cases of HCL,[1-5] and in some instances its use has been linked to prolonged clinical remission. However, although 80% of patients initially achieved normal peripheral blood counts following α-IFN therapy, the vast majority of them turned out to require further treatment.

The advent of more effective therapies for HCL, such as 2'-deoxycoformycin (DCF) and 2-chlorodeoxyadenosine (2-CdA), has now reduced the clinical role of α-IFN as primary treatment. The response rate to both DCF and 2-CdA is over 90%, and 75-85% of patients achieve apparent bone marrow remission.[6-14] Sensitive techniques suggest persistence of some residual hairy cells in many cases, but the relapse rate is generally low, and any way is lower than that following α-IFN. Both DCF and 2-CdA are generally well tolerated, but neutropenia may be a problem in cases of pre-existing marrow suppression. Although more extensive follow-up data exist for DCF,[13,15-21] either of these two agents can now be considered the treatment of choice for HCL, as the two drugs seem to offer similar benefits.

Regarding the administration of 2-CdA, a single course can be highly effective in any of the following three modalities: over 7 consecutive days at a dose of 0.1 mg/kg/day by continuous IV infusion,[10] or for 5 consecutive days at a dose of 0.15 mg/kg/day in a 2-hour infusion[21] or at a dose of 0.15 mg/kg in a 2-hour infusion once a week for 6 cycles.[22] Remissions after 2-CdA appear to be well maintained as evidenced by the relapse rates of several series.[20,21] However, results of a follow-up of more than 5 years are available for only one series.[19] In the present study, we reviewed the 9-year long-term follow-up data on 23 HCL patients who were treated with 2-CdA.

Design and Methods

Between January 1991 and February 1992, 23 HCL patients were treated with 2-CdA at our Institute. All patients had been previously treated with α-IFN and had relapsed after this treatment. Twenty-one were males and 2 females, with a median age of 59 years (range: 40-77). Table 1 summarizes the clinical characteristics of these patients. Criteria for inclusion in the study were the following: HCL diagnosis on the basis of the morphologic, immunologic, and bone

Table 1. Clinical characteristics of the 23 HCL patients.

No. of patients	23
Age (years):	
median	59
range	40-77
Sex	
M/F	21/2
Previous splenectomy	2
Splenomegaly	10
No splenomegaly	11

marrow features; anemia (Hb <10 g/dL) and/or neutropenia (neutrophils $<1.0\times10^9$/L) and/or thrombocytopenia (platelets $<100\times10^9$/L). The interval between diagnosis and treatment was 12 to 50 months.

2-CdA was administered as a single continuous IV infusion for 7 days at the dose of 0.1 mg/kg/day. The study was approved by the Institutional Review Board and informed consent according to the Declaration of Helsinki was obtained from all patients before the start of the treatment. Patients received antibiotic prophylaxis with ciprofloxacin. Complete blood counts with differential and chemistry panels were performed daily during the administration of 2-CdA. Subsequently, patients were monitored for the same parameters weekly for the first month, and then monthly for the first year. Bone marrow biopsies were done 2 months after treatment and annually thereafter. Biopsy samples were dacalcified, embedded in paraffin and sections were prepared for routine histology and immunohistochemical studies. In all biopsies, the following parameters were considered: global cellularity, percentage of hairy cells, hairy cell index (HCI) (defined as % cellularity $\times$ % HC/100), and amount and distribution of reticulin fibers. Minimal residual disease following therapy was detected by immunohistochemical means with both B-lineage- (such as anti-CD45RA and anti-CD20) and HCL- (DBA44) specific monoclonal antibodies.[23]

Response criteria

Complete response (CR) was defined as the absence of hairy cells in peripheral blood and bone marrow, disappearance of splenomegaly (when present), recovery of peripheral blood counts (hemoglobin >12 g/dL, platelets $>100\times10^9$/L, and neutrophils $>1.5\times10^9$/L). Additional requirements for CR were no hairy cells in bone marrow biopsies observed by routine histology and <1% hairy cells by immunostaining. Partial response (PR) was defined as a decrease of hairy cells in the bone marrow >50%, accompanied by restoration of peripheral blood counts (as defined for CR) persisting for at least 3 months. Relapse after CR was defined as the reappearance of hairy cells in the peripheral blood or bone marrow, development of cytopenias and/or splenomegaly. Relapse after PR was a >50% increase of residual disease.

Statistical analysis

The overall survival was measured from the start of treatment until death. Observations were censored at the date of the last follow-up for patients with no report of relapse or death. Relapse-free survival was calculated from the date of CR until either relapse or death from any cause. The overall survival and the relapse-free survival curves were determined according to the method of Kaplan and Meier.[24]

Results

Of the 23 patients, 19 (83%) achieved a CR and 4 (17%) a PR with an overall response rate (CR+PR) of 100%. Responses were rapid, with disappearance of both circulating hairy cells and spleen enlargement within 3 weeks of the end of 2-CdA infusion. Figure 1 shows the significant reduction of bone marrow infiltration (HCI $\leq$ 0.01) at the end of 2-CdA treatment. The 4 PRs have obtained a HCI of 0.02, 0.16, 0.05, and 0.15. After a median follow-up of 102 months (range: 96-108), there have been 9 (39%) relapses. In particular, in the PR subset we observed 4/4 (100%) relapses occurring within the first 4 years of follow-up (at 16, 18, 41, and 45 months). In the group of patients who obtained a CR there were 5/19 (26%) relapses; all these relapses occurred between 54 and 86 months. Globally, the median time to relapse was 54 months (range: 16-86).

All the patients who relapsed were re-treated with 2-CdA at the dose of 0.15 mg/kg/day for 5 days in a 2-hour infusion: 6/9 (67%) then obtained a second CR and 2/9 (22%) achieved PR; one patient (who had been in PR following the first line of 2-CdA) died 6 months after the second line due to infectious complications associated with severe neutropenia. The two patients who have had a PR belonged to the subset of patients who achieved a CR to the first treatment with 2-CdA. The median duration of this second response was 48 months (range: 22-80). All but one of these patients still maintain the second response to 2-CdA. The only patient who relapsed twice had achieved a second CR, once again induced by 2-CdA, which lasted 80 months (after the first line of 2-CdA he had had a PR with disease progression after 18 months). At this point, he was re-treated with DCF at a dose of 4 mg/m^2 every 2 weeks for a total of eight administrations (the last two monthly) and achieved a new CR which he has currently maintained for 8 months.

There have been 2 deaths, one from neutropenia-related infection after the second line of 2-CdA and another from acute hepatitis which occurred in a patient in CR 30 months after the end of the first line 2-CdA. No patient has developed a secondary malignancy. The 9-year projected overall (Figure 2) and relapse-free (Figure 3) survivals are 91% and 70%, respectively. The majority of patients experienced little or no toxicity from either treatment as reported elsewhere.[25,26] However, it must be noted that most patients received G-CSF during treatment, including the elderly, heavily pretreated one who actually died of infection.

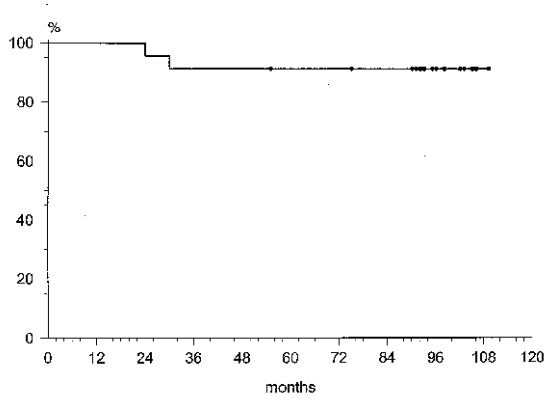

Figure 1. Overall survival curve of all 23 HCL patients.

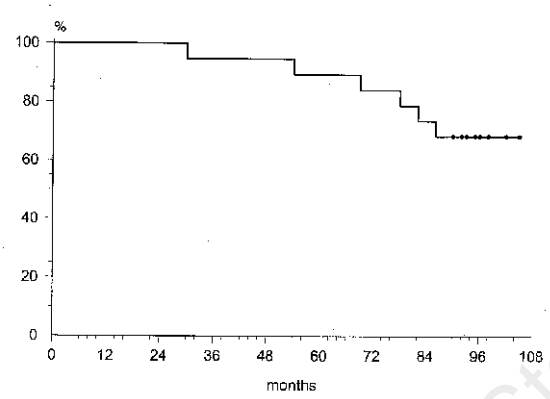

Figure 2. Relapse-free survival curve of 19 patients who achieved CR.

Discussion

Nowadays, the principal choice for the treatment of HCL is between DCF and 2-CdA. The overall response rates to DCF and 2-CdA are around 90%, with low occurrence of early relapses at least in the short-term. 2-CdA may produce a slightly higher response rate, but trials have not been comparative and differences appear small. More data exist for DCF, with several series evidencing that most patients remain in remission beyond 4-5 years.[15-19] Following relapse, a proportion of patients respond to retreatment with the same agent.[13,19,26] It has been reported that patients primarily or secondarily resistant to DCF may respond to 2-CdA, but such responses are not always seen.[27,28]

This study extends the results reported by other investigators[19] of long-term responders among HCL patients who undergo 2-CdA treatment. In fact, the present series, with a median follow-up of 8.5 years (range, 8-9 years), is among the longest in the literature. Considering that all patients were pretreated, having already received α-IFN at the time of diagnosis, the overall response rate of 100% with a CR rate of 83% seems highly promising. The percentage of relapse-free survival was 70% at 9 years, with a total of 9/23 (39%) relapses with different timing for PRs (within 4 years) and CRs (after 54 months and the last one after 86 months). It is interesting to note that in the last 2 years of follow-up no relapses were observed. At 9 years, 12/23 (52%) are still in continuous CR after the first line of 2-CdA; in addition, with this long-term follow-up, 18/23 (78%) are still in CR (12 with the first line and 6 with the second line of 2-CdA). In this series no patients have developed a secondary malignancy, and one of the two deaths was from an unrelated cause (acute hepatitis more than 2 years after the end of 2-CdA treatment). The absence of secondary neoplasms is substantially in keeping with data from other authors who noted no evidence that the frequency of secondary malignancies might in any way increase due to 2-CdA treatment.[29-31]

It is clear that 2-CdA produces durable remissions in most HCL patients. However, it is still unclear whether some HCL patients can be considered cured by this single agent. Until 7 years there is no plateau in the relapse-free survival, but about 50% of the patients have remained in remission for more than 8 years. Overall, it can be stated that it is possible to achieve long-lasting CRs after a single course of purine analog, and those patients who relapse can be successfully re-treated with another cycle.

A possibly sound sequential treatment aimed at eradicating HCL in most patients could be induction with 2-CdA followed by maintenance therapy utilizing new biological approaches such as anti-CD20 monoclonal antibody[32] or recombinant immunotoxins containing truncated pseudomonas exotoxin and targeting either CD25 or CD22.[33]

Contributions and Acknowledgments

PLZ was the principal investigator involved in the conception of the study, its design, and the writing of the paper. MM and MB helped the principal investigator (PLZ) with data analysis interpretation. VS, MT, and CC collected the study data. SP, MP and SP followed all the histopathologic studies. ST critically revised the paper and gave the final approval for its submission.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

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Potential implications for clinical practice

- In the light of our long-term update, we conclude that nowadays 2-CdA represents the best first-line treatment for patients with HCL.