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 PICCOLO, 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, 25% 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 retreated 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.

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marrow features; anemia (Hb <10 g/dL) and/or neutropenia (neutrophils <1.0×10^9/L) and/or thrombocytopenia (platelets <100×10^9/L). The interval between diagnosis and treatment was 12 to 50 months. Relapse after PR was a >50% increase in 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 (HCl ≤ 0.01) at the end of 2-CdA treatment. The 4 PRs have obtained a HCl 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.
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. Following relapse, a proportion of patients respond to retreatment with the same agent. It has been reported that patients primarily or secondarily resistant to DCF may respond to 2-CdA, but such responses are not always seen.

This study extends the results reported by other investigators 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.

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 or recombinant immunotoxins containing truncated pseudomonas exotoxin and targeting either CD25 or CD22.

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.
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