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Long-term follow-up of front-line treatment of hairy cell leukemia with 2-chlorodeoxyadenosine

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A B S T R A C T

Background and Objectives. Although remission of hairy cell leukemia (HCL) after treatment with 2-chlorodeoxyadenosine (2-CdA) appears to be long lasting, few reports currently provide results from follow-up exceeding 5 years.

Design and Methods. We reviewed our HCL patients treated with front-line 2-CdA (by 2-hour infusion) either for 5 consecutive days at 0.14 mg/kg/day (daily subset, n=21) or once a week at 0.14 mg/kg for 5 cycles (weekly subset, n=16).

Results. Of the 37 eligible patients, 30 (81%) achieved complete response (CR) and 7 (19%) partial response (PR) (overall response rate, 100%); identical response rates were recorded in the daily and weekly subsets. After a median follow-up of 122 months (range, 54–156), the overall relapse rate was 27% (8/30): 24% (4/17) had relapsed in the subset treated daily whereas 30% (4/13) had done so in the subset treated weekly (*p*=ns). The projected 13-year overall and the relapse-free survivals are 96% and 52%, respectively. In terms of hematologic toxicity, the weekly 2-CdA schedule was associated with significantly fewer cases of grade 3-4 neutropenia.

Interpretation and Conclusions. In HCL patients, a single dose of 2-CdA induces a long-term CR. Over 90% of patients are alive 13 years later and over 50% of patients appear to be clinically cured by this treatment. The weekly schedule seems to be a safer option for neutropenic HCL patients, while apparently providing equivalent results in terms of response rates and long-term outcome.

Key words: hairy cell leukemia, 2-chlorodeoxyadenosine, neutropenia, hematologic toxicity, long-term follow-up.

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In the last 20 years the therapeutic approach to hairy cell leukemia (HCL) has shifted radically from splenectomy and α-interferon[1-5] to purine analogs such as pentostatin and 2-chlorodeoxyadenosine (2-CdA),[6-14] while the anti-CD20 monoclonal antibody[15-17] has recently shown interesting preliminary results. Both pentostatin and 2-CdA produce response rates over 90%, with 75%–85% of patients achieving apparent bone marrow remission.[6-14] Although sensitive immunologic or molecular techniques often reveal persistence of some residual hairy cells, relapse rates are generally lower than those encountered after α-IFN. A single course of 2-CdA can be highly effective given in any of three administration modalities (7 consecutive days at 0.1 mg/kg/day by continuous i.v. infusion;[10] 5 consecutive days at 0.14 mg/kg/day in a 2-hour infusion;[18,20] six weekly cycles of 0.14 mg/kg in a 2-hour infusion).[19] Although several series indicate that remissions after 2-CdA appear to be well maintained,[21-23] only a few reports currently provide results of follow-up exceeding 5 years.[24-26] In the present study, we review the long-term follow-up data of a series of HCL patients treated with either daily or weekly front-line 2-CdA over a 13-year period in the context of two different trials.

Design and Methods

Protocols and eligibility criteria

The present analysis regards all HCL patients treated with 2-CdA at the Seràgnoli Institute with at least 5 years of recorded follow-up. Between January 1991 and January 1999, two different 2-CdA administration modalities were used as front-line

treatment for HCL in the context of two non-randomized studies: 5 consecutive days at 0.14 mg/kg/day in a 2-hour infusion (daily subset, treated between January 1991 and 1999); and at a dose of 0.14 mg/kg in a 2-hour infusion once a week for 5 weeks (weekly subset, casually selected since 1994). Eligibility criteria for either treatment protocol were as follows: HCL diagnosis on the basis of the morphologic, immunologic, and bone 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 1 to 5 months. Approval was obtained from the Institutional Review Board for both study protocols; informed consent was provided according to the Declaration of Helsinki and was obtained from all patients before the start of the treatment. During treatment, complete blood counts with differential and chemistry panels were performed daily or weekly (in correspondence with the administration schedule). Both protocols included antibiotic prophylaxis with ciprofloxacin. Subsequently, all 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 and 4 months after treatment and annually thereafter. Biopsy samples were decalcified, embedded in paraffin and sections were prepared for routine histology and immunohistochemical studies. The following parameters were considered in all biopsies: global cellularity, percentage of hairy cells, hairy cell index (HCI) (defined as % cellularity × % 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.[27]

Response criteria

Complete response (CR) was defined as the absence of hairy cells in peripheral blood and bone marrow, disappearance of splenomegaly (when present), and 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 >50% decrease of hairy cells in the bone marrow, accompanied by recovery 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 on physical examination. Relapse after PR was a >50% increase of residual disease.

Table 1. Baseline characteristics of the 37 HCL patients.

	Daily subset (21 pts.)	*Weekly subset (16 pts.)*	*Overall (37 pts.)*
Age (years)			
Median	55	54	54
Range	37–76	38–75	37–76
Males	16 (76%)	13 (81%)	29 (78%)
Splenomegaly	7 (33%)	5 (31%)	12 (32%)
Median time from HCL diagnosis (months)	3	3	3
Median absolute neutrophil count, $\times10^9$/L (range)	0.9 (0.5–1.3)	0.8 (0.4–1.2)	0.9 (0.4–1.3)
Median absolute lymphocyte count, $\times10^9$/L (range)	0.7 (0.3–1.1)	0.8 (0.4–1.2)	0.8 (0.3–1.2)
Median hemoglobin level, g/dL (range)	12.9 (12–14.1)	13.0 (12.2–14.3)	12.9 (12–14.3)
Median platelet count, $\times10^9$/L (range)	118 (78–149)	122 (85–154)	120 (78–154)

Statistical analysis

Overall survival was measured from 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. Overall survival and the relapse-free survival curves were determined according to the method of Kaplan and Meier.[28]

Results

Table 1 summarizes the baseline characteristics of the 37 eligible patients divided according to 2-CdA administration subset; these two groups turned out to be well matched in terms of clinical and hematologic parameters at diagnosis. Table 2 reports response rates, as well as relapse rates among patients who achieved CR. The CR and overall response (CR+PR) rates of 81% and 100%, respectively, recorded in the entire sample were also reproduced in each of the two treatment subsets. Responses were rapid, with disappearance of both circulating hairy cells and splenomegaly always occurring within 3 weeks of the end of 2-CdA infusion. After a median follow-up of 122 months (range,

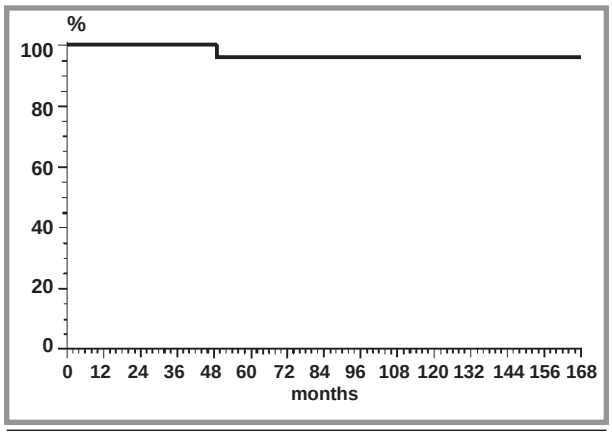

Figure 1. Overall survival curve of all 37 HCL patients.

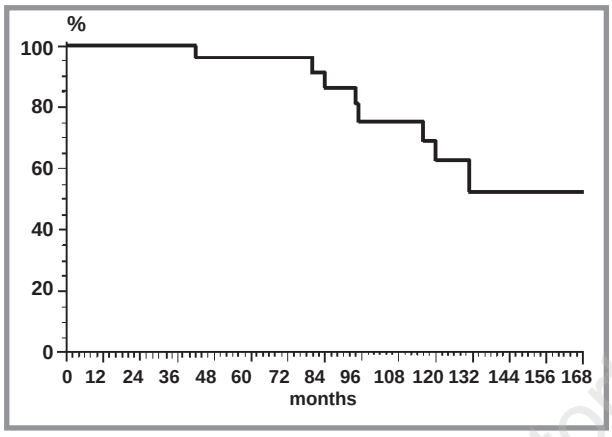

Figure 2. Relapse-free survival curve of the 30 patients who achieved CR.

54–156), there have been 8 (27%) relapses among patients who achieved CR, including 4/13 (30%) in the weekly subset and 4/17 (24%) in the daily subset (p = ns). All these relapses occurred between 42 and 131 months: at 42, 80, 84, and 95 months in the weekly subset, and at 94, 116, 120, and 131 months in the daily subset. All relapsed patients were re-treated with 2-CdA: 6/8 (75%) then achieved a second CR and 2/8 obtained (25%) PR. The median duration of this second response was 58 months (range: 32-90). Four of 6 (67%) patients have maintained their second CR; the remaining two relapsed after 46 and 80 months in second CR, and they then both attained a third CR after treatment with pentostatin at a dose of 4 mg/m^2 every 2 weeks for a total of eight administrations (the last two monthly). One patient died from lung cancer 49 months after diagnosis having achieved a first CR (weekly subset). All 7 patients who initially obtained PR had disease progression within the first 3 years; they were retreated with 2-CdA (5 patients) and with 2-CdA plus rituximab (sequentially) (2 patients) and all of them obtained a response (5 CR and 2 PR). The 13-

Table 2. Response to 2-CdA and relapse rates among patients who achieved CR.

	Daily subset (21 patients)	*Weekly subset (16 patients)*	*Overall (37 patients)*
CR rate	81% (17/21)	81% (13/16)	81% (30/37)
PR rate	19% (4/21)	19% (3/16)	19% (7/37)
Response rate [CR+PR]	100% (21/21)	100% (16/16)	100% (37/37)
Relapse rate (in CR)	24% (4/17)	30% (4/13)	27% (8/30)

year projected overall (Figure 1) and relapse-free (Figure 2) survival rates are 96% and 52%, respectively.

The majority of patients experienced little or no toxicity from either treatment. However, as regards hematologic side effects, daily administration was associated with a significantly higher rate of grade 3–4 neutropenia (72% [15/21] vs. 38% [6/16]; $p = 0.039$); time to neutrophil recovery was similar in the two treatment groups. Concerning infection, 2 patients treated with the daily schedule required systemic antibiotics for Gram-positive bacterial infections. Grade 3–4 thrombocytopenia rates were similar in the daily and weekly subsets (19% [3/16] vs. 14% [3/21]; p = ns). Only one second malignancy occurred (*see above*).

Discussion

Only a few reports[24-26] are available of long-term responders to 2-CdA treatment for HCL. The present analysis extends the follow-up of 37 patients followed for at least 5 years after front-line treatment at the Seràgnoli Institute with either weekly or daily administration of 2-CdA. With a median follow-up of 10 years (range, 5-13 years), this series is among the longest in the literature. Our results reinforce the concept that while weekly and daily administration of 2-CdA are both effective treatment options, the weekly schedule is safer for patients presenting with marked neutropenia.

It is not currently known whether pentostatin or 2-CdA should be the treatment of choice for patients with HCL, given the similar response rates and similar toxicity produced by these two drugs. Initially, the high CR rates reported after a single course of 2-CdA treatment encouraged many physicians to believe that this strategy might by itself prove curative in the majority of patients.[6-14] With further experience, however,

relapses were noted in a minority of patients treated with 2-CdA and several reports indicated that patients treated with 2-CdA who clinically appeared to be in CR had evidence of minimal residual disease when tested by immunologic or molecular techniques. While it is clear that the modern treatments for HCL are not generally curative in the sense of obliterating the neoplastic clone, they are extremely effective in inducing very long-lasting clinical remissions.[24-26] In terms of outcome, our findings are broadly in line with this picture. After 5 to 12 years follow-up, 76% (28/37) of our patients are still in CR (22 after first-line and 6 after second-line 2-CdA). In our series, only one patient developed a secondary malignancy. Thus, our long-term follow up confirms the impression that 2-CdA produces durable remissions in most cases, and that those patients who do relapse can often be successfully re-treated with the same drug.

Alternative routes and schedules of administration to the standard 7-day continuous intravenous infusion have been explored. These alternatives include a 5-day 2-hour bolus infusion,[18] a weekly 2-hour bolus infusion for 5 weeks[19] and subcutaneous administration.[20] Response rates after the 2-hour bolus appear to be similar to those achieved with the standard 7-day continuous infusion.[10] A few reports suggest that weekly 2-hour bolus infusion of 2-CdA is as effective as the standard daily schedule, and that it is probably safer as it seems to induce less severe and persistent neutropenia.[19,29] We compared the weekly and daily schedules—administered in the context of two different non-randomized studies conducted in our Institute—in terms of CR rate, long-term response, toxicity, and survival. In our series, the two 2-CdA administration schedules showed equivalent CR rates (both 81%) with similar percentages of subsequent relapses (30% and 24% with the weekly and daily schedules, respectively). In addition, all patients obtained at least a PR, regardless of the schedule. However, the weekly schedule was associated with significantly less hematologic toxicity, i.e. neutropenia.

Our data from non-randomized groups of limited size with heterogeneous long-term follow up can only provide suggestive indications. However, our long-term follow-up data broadly confirm the concept[19,29] that while the weekly schedule seems to be as effective as the daily one in terms of response rates and eventual outcome, it almost certainly provides a safer option in terms of risk of neutropenia. Thus, we think that the option of weekly administration should be seriously considered for HCL patients who are profoundly neutropenic at the time of diagnosis.

Future research will include clinical testing of an oral formulation of 2-CdA and clinical trials exploring approaches for patients with minimal residual disease (such as anti-CD20 monoclonal antibody, anti-CD22 monoclonal antibody, recombinant immunotoxin BL22, denileukin diftitox)[15-17,30,31] to prevent relapse.

PLZ was the principal investigator involved in the conception of the study, its design, and PLZ wrote the paper. SP was involved in the histological review. MT, EM, VS, LA, GM, and AG collected the study data. MB critically revised the paper and gave the final approval for its pubblication. Zinzani PL was primarily responsible for the publication.PLZ was primarily responsible for Tables 1-3 and for Figures 1-2. The authors reported no potential conflicts of interest.

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