Cladribine in a weekly versus daily schedule for untreated active hairy cell leukemia: final report from the Polish Adult Leukemia Group (PALG) of a prospective, randomized, multicenter trial.

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Abstract
Cladribine (2-chlorodeoxyadenosine, 2-CdA) treatment-associated infections may shorten potentially long-term survival in hairy cell leukemia (HCL). In search of optimal mode of 2-CdA administration, 132 patients with untreated HCL were randomized to receive either standard 5-day 2-CdA protocol or novel schedule of six weekly 2-CdA infusions suggested to be less toxic. Analysis of treatment response confirmed similar complete remission rates, overall response rates, progression-free survival and overall survival in both 2-CdA protocols. However, we did not observe lower toxicity of weekly schedule. Of special interest, no significant differences were found in rate of grade 3/4 infections (18% for daily and 26% for weekly protocol, difference=-8.2% (95% confidence interval -23.2 to 6.9%), p=0.28) and rate of septic deaths (3% for daily and 2% for weekly protocol, difference=1.4% (95% confidence interval -4.3 to 7.0%), p=0.64). In conclusion, HCL treatment with weekly 2-CdA infusions is equally effective, but no safer than standard 5-day 2-CdA protocol.

Introduction
Cladribine (2-chlorodeoxyadenosine, 2-CdA) belongs to standard therapeutic options for hairy cell leukemia (HCL). In chemotherapy-naïve HCL one course of 2-CdA induces complete response (CR) and long-term survival in the vast majority of patients (1-5). Given this considerable clinical efficacy, the major challenge regarding 2-CdA therapy is reduction of side-effects, especially severe infections that may lead to septic deaths. Lauria et al. (6) suggested that a novel schedule based on six weekly 2-hour 2-CdA infusions could be as effective as standard 7-day and 5-day protocols but associated with less neutropenia and life-threatening infections. To test potential clinical benefit of the weekly schedule, in 1998 Polish Adult Leukemia
Group (PALG) initiated a prospective multicenter, randomized comparison with 5-day 2-CdA infusion that is the standard treatment of active HCL in Poland.

**Study design**

The study was carried out at 14 hematology centers, with central randomization and data management performed in the Department of Hematology of Medical University of Lodz. The study was approved by the Ethics Committee of the Medical University of Lodz, and all patients gave informed consent.

**Eligibility criteria**

Patients with untreated, active HCL, WHO scale performance status better than grade 4, normal liver and renal function, without secondary neoplasm, aged more than 18 years were considered eligible. The diagnosis of HCL and the criteria of activity of disease were defined as previously reported (7).

**Treatment**

Patients were randomly assigned to one of the following 2-CdA schedules: (a) 2-CdA at 0.12 mg/kg in 2-hour intravenous infusion for 5 days (further referred as the daily schedule); (b) 2-CdA at 0.12 mg/kg in 2-hour intravenous infusion once a week for 6 weeks (further referred as the weekly schedule). In patients who achieved CR after the first cycle, treatment was stopped. In patients with PR treatment could be continued until maximal response or stopped according to the decision of the treating physician, and in the case of no response (NR) or progression of the disease the treatment was changed. No antibiotic or hematopoietic growth factor prophylaxis was given.

**Study end points**

The study objective was to verify the hypothesis that the 2-CdA weekly schedule has similar efficacy but lower early toxicity than the 5-day schedule. The primary end points were CR at three months after completion of the 2-CdA therapy and treatment-related grade III/IV infections during four months from start of 2-CdA. The secondary end points included overall response rate (ORR), progression-free survival (PFS), OS, and other grade 3/4 side-effects. Criteria for response were defined according to Grever et al.(8) and NCI guidelines (9), and toxicity according to WHO criteria(10). Deaths that occurred during four months from start of 2-CdA were defined as early deaths (ED).
Statistical analysis

Calculation of sample size was based on previous reports indicating that identical CR rate of 75%, but different major infection rate of 28% and of 8% may be expected with 5-day and weekly 2-CdA schedule, respectively (5,11). Fifty-four patients were required to be assigned to each treatment arm to detect a decrease of 25% from 75% CR rate with error levels of $\alpha=0.05$ and $\beta=0.2$ for a two-sided test. Taking into account possible drop-outs, accrual was increased by 20% resulting in a requirement of 65 patients per arm. Treatment groups were compared using the Mann-Whitney test for continuous data, and the Chi-squared test for categorical data. Difference between proportions, and associated confidence intervals, were calculated by standard methods. OS was defined as time from randomization to death, and PFS as time from randomization to progression or death. PFS and OS curves were plotted using the Kaplan-Meier method and probabilities of PFS and OS were compared by the log-rank test (12,13). $p<0.05$ was considered statistically significant.

Results and Discussion

Between the 1st January 1998 and the 31st September 2005, 132 patients with untreated, active HCL from 14 centers were randomized to receive either daily (68 patients) or weekly (64 patients) 2-CdA protocols. Sixteen patients were excluded from analysis due to misdiagnosis (4 patients), not met eligibility criteria (6 patients), withdrawal of the consent (3 patients) and drop-out before beginning of the treatment (2 patients). Baseline characteristics of 116 patients assessed for response, toxicity and survival are shown in Table 1.

We found that response to chemotherapy was comparable in both treatment arms (Fig.1A). The response was assessed after similar total number of administered treatment courses in both cohorts, with 97(84%) patients who received only one 2-CdA course. In the group of daily 2-CdA, there were 47(76%) patients with CR, 12(19%) patients with PR, one patient (2%) with NR and two ED compared with 39(72%) patients with CR, 10(19%) patients with PR, 4(7%) with NR and one ED (2%) in the weekly schedule. Therefore, daily and weekly protocols gave similar high CR rate ($p=0.86$) and ORR (95% vs. 91%, $p=0.41$). Moreover, survival analysis did not produce significant differences between the 2-CdA protocols (Fig. 1B and C). The estimated 6.5 year OS was 91% and 88% ($p=0.40$) and median PFS was 4.3 years (95%CI=3.3-5.2) and 5.1 years (95%CI=4.7-5.6) ($p=0.28$) for daily and weekly
schedule, respectively. Our findings on equivalent efficacy of these 2-CdA schedules are in accordance with retrospective non-randomized comparison on 37 patients published before (14). DCF, another purine nucleoside analog used in the treatment of HCL, seems to have similar efficacy and toxicity as 2-CdA, although direct randomized comparison of the two agents has not yet been performed (8,15,16).

In contrast to previous suggestions (6,11,14), our work did not confirm reduced toxicity of weekly 2-CdA schedule. A total of 25 grade 3/4 infections were observed in 24 patients including one subject treated with weekly protocol who developed two separate infectious episodes (acute bronchitis and FUO). Most importantly, the prevalence of grade 3/4 infections did not differ regarding treatment arm (18% for daily and 26% for weekly 2-CdA protocol, difference=-8.2% (95%CI -23.2 to 6.9 %), p=0.28) (Table 1). The time to the infection onset and the time of infection duration were comparable in the two schedules (Table 1). Also the rates of major types of grade 3/4 infections were similar in both protocols (Table 1). Moreover, daily and weekly 2-CdA schedules gave comparable prevalence of severe infections even if analyses were restricted to patients with pre-treatment neutropenia below 1.0 G/l (17% vs. 26%, difference=-9.8%,(95%CI –24.6 to 5.0%), p=0.32) and below 0.5 G/l (21 vs. 26%, difference=-5.0% (95%CI 20.4 to 10.5%), p=0.56). This similar risk of severe infections is in line with identical rates of progression of neutropenia on treatment (47% for both treatment arms, difference=0.48% (95%CI –17.7 to 18.7%), p=0.97) and comparable rates of neutropenia below 0.5 G/L and 1.0 G/L (Table 1). The comparison of other grade 3/4 side-effects including thrombocytopenia and anemia following 2-CdA therapy as well as transfusion requirements did not show significant differences (Table 1).

Secondary neoplasia is a major complication that can be related to both the biology of HCL and immunosupression caused by chemotherapy. In this study, seven second cancers were diagnosed including acute myeloid leukemia (AML), renal cell cancer, ovarian cancer and skin carcinoma basocellullare in daily 2-CdA schedule, and breast cancer, prostate cancer and unknown primary adenocarcinoma in weekly schedule. The median time to the diagnosis of the second cancer reached 2.3 years (range 0.2 - 4.2 years).

Special attention was paid to the analysis of causes of mortality in the study. A total of six deaths were recorded during the follow-up period including four deaths in daily and two in weekly 2-CdA protocol groups. Three deaths were classified as
ED including 2(3%) in daily and 1(2%) in weekly 2-CdA schedule, difference=1.4% (95% confidence interval -4.3 to 7.0%), p=0.64). The cause of all EDs were infectious complications (pneumonia in one and sepsis in two other patients). The time from first day of 2-CdA treatment to death was three, 31 and 60 days. All three patients had neutropenia below 0.25 G/L during infection onset that did not improve to the last blood count analysis. Systematic blood cultures revealed infection with Hafnia alvei in one patient, while were negative in the other two patients. Among three deaths that occurred late in observation two were related to infections during HCL progression and one to secondary AML. Therefore, our study confirm that septic deaths are major cause of early mortality in HCL treated with 2-CdA, although decrease in therapy density does not seem to solve this problem. However, it should be noted that the total dose of 2-CdA was higher in weekly than in 5-day schedule (six vs. five infusions) that could influence the observed results.

In conclusion, the results of our randomized trial indicate that weekly 2-CdA infusions for 6 weeks used in the treatment of active HCL are equally effective, but not less toxic than standard 5-day 2-CdA protocol. Further studies in search for strategies to decrease risk of life-threatening infections complicating the treatment of HCL with 2-CdA are required.

Acknowledgements

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Preliminary results of this study were presented at 46th Annual Meeting of the American Society of Hematology, San Diego, CA, December 4-7, 2004 (17), and at the 48th Annual Meeting of the American Society of Hematology, Orlando, Florida, December 9-12, 2006 (18).

TR designed and supervised the trial and wrote the report, KJ performed statistical analysis and wrote the report, JG-T was responsible for monitoring of the trial,
management of the data at the coordinating center and wrote the report, JZB, MK, JD-T, EW, AZ, JD, AD, MW, BZ, MC, AK, AH, KL, BS-H, KS, KG, ABS, WN, KZ, LM-P, JK, JS, KW, IS, LK, BC were responsible for patients’ accrual, monitoring and management of the clinical data at their referring centers.

References

Table 1. Comparison of baseline characteristics and grade 3/4 treatment-related side effects in patients randomized to daily and weekly schedules of 2-CdA administration.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>2-CdA daily n = 62</th>
<th>2-CdA weekly n = 54</th>
<th>p</th>
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<tbody>
<tr>
<td><strong>Patient characteristics</strong></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Median age, years, (range)</td>
<td>53 (27-78)</td>
<td>57 (25-86)</td>
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<tr>
<td>Males, no.(%)</td>
<td>41 (66)</td>
<td>37 (68)</td>
<td>0.74</td>
</tr>
<tr>
<td>Median time from diagnosis, months (range)</td>
<td>0.4 (0-37.8)</td>
<td>0.1 (0-13.4)</td>
<td>0.21</td>
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<tr>
<td>Median white cell count, x G/L (range)</td>
<td>2.2 (0.7-30.0)</td>
<td>2.8 (0.7-34.0)</td>
<td>0.09</td>
</tr>
<tr>
<td>Median absolute neutrophil count, x G/L (range)</td>
<td>0.42 (0.0-4.5)</td>
<td>0.66 (0.1-2.0)</td>
<td>0.48</td>
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<tr>
<td>Median hemoglobin g/L, (range)</td>
<td>9.9 (3.7-15.2)</td>
<td>10.8 (4.3-16.4)</td>
<td>0.42</td>
</tr>
<tr>
<td>Median platelets x G/L, (range)</td>
<td>66 (1-301)</td>
<td>86 (2-238)</td>
<td>0.02</td>
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<tr>
<td>Lymphadenopathy, no. (%)</td>
<td>8(13)</td>
<td>8(15)</td>
<td>0.76</td>
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<td>Splenomegaly, no. (%)</td>
<td>38 (63)</td>
<td>31(57)</td>
<td>0.68</td>
</tr>
<tr>
<td>Hepatomegaly, no. (%)</td>
<td>5 (8)</td>
<td>12 (22)</td>
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<td><strong>Treatment side-effects</strong></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<td>Progression of neutropenia, no. (%)</td>
<td>29 (47)</td>
<td>25 (47)</td>
<td>0.97</td>
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<td>Neutropenia below 0.5 G/L, no. (%)</td>
<td>36 (58)</td>
<td>28 (52)</td>
<td>0.27</td>
</tr>
<tr>
<td>Neutropenia below 1.0 G/L, no. (%)</td>
<td>38 (61)</td>
<td>28 (52)</td>
<td>0.20</td>
</tr>
<tr>
<td>Progression of thrombocytopenia, no. (%)</td>
<td>10 (16)</td>
<td>9 (17)</td>
<td>0.93</td>
</tr>
<tr>
<td>Platelets transfusions, units</td>
<td>47</td>
<td>39</td>
<td>0.21</td>
</tr>
<tr>
<td>Progression of anemia, no. (%)</td>
<td>9 (15)</td>
<td>10 (19)</td>
<td>0.58</td>
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<td>Red cell transfusions, units</td>
<td>47</td>
<td>40</td>
<td>0.82</td>
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<td>All Infections including FUO, no. (%)</td>
<td>11 (18)</td>
<td>14 (26)</td>
<td>0.28</td>
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<tr>
<td>Pneumonia, no. (%)</td>
<td>5 (8)</td>
<td>4 (7)</td>
<td>0.87</td>
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<tr>
<td>Urinary tract infections, no. (%)</td>
<td>1(2)</td>
<td>2 (4)</td>
<td>0.49</td>
</tr>
<tr>
<td>Other infections, no. (%)</td>
<td>3 (5)</td>
<td>5 (9)</td>
<td>0.37</td>
</tr>
<tr>
<td>Fever of unknown origin (FUO), no. (%)</td>
<td>2 (3)</td>
<td>5 (9)</td>
<td>0.18</td>
</tr>
<tr>
<td>Time to infection, days (range)</td>
<td>6 (1-14)</td>
<td>11 (3-28)</td>
<td>0.09</td>
</tr>
<tr>
<td>Duration of infection, days (range)</td>
<td>5 (1-60)</td>
<td>13 (3-28)</td>
<td>0.27</td>
</tr>
<tr>
<td>Septic deaths, no. (%)</td>
<td>2 (3)</td>
<td>1 (2)</td>
<td>0.64</td>
</tr>
<tr>
<td>Allergic symptoms, no. (%)</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>0.49</td>
</tr>
<tr>
<td>Second malignancies, no. (%)</td>
<td>4 (6)</td>
<td>3 (6)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

2-CdA - 2-chlorodeoxyadenosine, FUO - fever of unknown origin, NA – not applicable
Figure 1. Comparison of clinical activities of two schedules of 2-CdA administration in newly diagnosed patients with hairy cell leukemia tested in the study. (A) Response to 2-CdA therapy (B) Overall survival analysis (C) Progression-free survival analysis.
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