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RETROSPECTIVE ANALYSIS OF 34 CASES OF HAIRY CELL LEUKEMIA TREATED WITH INTERFERON-α AND/OR 2-CHLORODEOXYADENOSINE

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ABSTRACT

The aim of the present study was to compare the outcome of patients affected by typical hairy cell leukemia (HCL) treated with interferon-α (IFN-α) and/or 2-chlorodeoxyadenosine (2CdA). Thirty-four consecutive patients were enrolled in the study. IFN was administered in 26 cases as first line therapy at a dose of 3 MU every other day for 12 months. 2CdA was given in 8 cases as first-line and in 14 cases as second-line therapy in patients resistant to (2 cases) or relapsed after (12 cases) IFN. The treatment schedule for 2CdA was 0.1 mg/kg/daily for 7 days for 1 cycle (17 patients) or 2 cycles (5 patients). Complete (CR) and partial remission (PR) were 19% and 58%, respectively, for IFN, 75% and 25% for 2CdA in first-line therapy, 86% and 14% for 2CdA in second-line therapy. Median progression-free survival for IFN patients was 19 months and no statistical advantage was detected for those who achieved a CR vs those in PR. In the group treated with 2CdA, only 1 patient (4%) relapsed after a median follow-up of 14 months. At a median follow-up of 59 months (range 4-134), overall survival of all 34 patients was 97%, with only 1 patient having died of an acute leukemia. Our results confirm the favorable outcome currently expected for HCL and emphasize the therapeutic activity of 2CdA in the treatment of this disease.

Key words: hairy-cell leukemia treatment, IFN-α

Up to two decades ago the treatment of hairy cell leukemia (HCL) produced very disappointing results: median patient survival was only a few years. The introduction of the interferons (IFN) in 1984[1] and of the new purine analogues deoxycoformycin (DCF)[2] and 2-chlorodeoxyadenosine (2CdA)[3] in the early nineties dramatically improved the outcome of HCL patients, allowing a less complex and more optimistic approach to this disease.

Here we report a retrospective analysis of 34 patients with typical HCL, selected for treatment with IFN-α or 2CdA, observed between June 1985 and August 1996. The aim of the study was to evaluate outcome in relation to the different therapeutic regimens applied (IFN vs 2CdA).

Patients and Methods

Before June 1993, all the patients observed (26 cases) were given IFN-α as first-line treatment (IFN group), at a dose of 3 MU s.c. every other day for 12 months. No maintenance therapy was administered to responsive patients. After June 1993, 2CdA was employed as first-line treatment in 8 patients (group A) and as second-line treatment in 14 others with recurrent (12 cases) or refractory (2 cases) HCL following IFN (group B). 2CdA was administered as a 2-hour iv infusion at a dose of 0.1 mg/kg daily for 7 days for one course (17 patients) or two (5 patients). Response criteria were those described by Tallman *et al.*[4] Progression-free survival (PFS) was calculated in responding patients from the end of the therapeutic program, while overall survival (OS) was calculated in all patients from diagnosis. Both parameters were evaluated using the Kaplan-Meier method. The differences among groups were compared with the log-rank test.

Results

The patients' clinical and hematologic features before treatment are reported in Table 1. All patients were evaluable for response.

IFN. Twenty patients (77%) achieved a response, complete in 5 (19%) and partial in 15 (58%). Six patients (23%) were considered as non responders. No major hematological toxicity was observed during IFN treatment. In 4 patients with neutrophil counts lower than 1×10^9/L at the beginning of IFN treatment, filgrastim 300 µg s.c. was given every other day for 12 to 20 times. Extrahematological toxicity consisted of flu-like syndrome (14 cases), fever of unknown origin (FUO) (6 cases), I°-II° WHO grade weakness (5 cases) and alopecia (3 cases), weight loss (2 cases), pruritus (2 cases), sweating (2 cases). After a median follow-up of 19

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Table 1. Main clinical and hematologic features before treatment with IFN-α and 2CdA, response to therapy.

	IFN group	*2CdA group A*	*2CdA group B*
No. of patients	26	8	14
Age, median (range), years	48 (28-73)	48 (41-65)	45.5 (35-73)
Male/female	18/8	5/3	12/2
Infective disease (%)	7 (27)	0	1 (7)
Symptoms (%)	6 (23)	1 (12.5)	2 (14)
Splenomegaly (%)	18 (69)	4 (50)	6 (43)
Lymphadenopathies (%)	1 (4)	0	1 (7)
Hemoglobin, g/dL, median (range)	11 (4.5-16.4)	11.5 (5.3-12.9)	12.4 (5-14.9)
Platelets x 10^9/L, median (range)	62 (22-237)	67.5 (29-119)	76.5 (27-144)
Pts with platelets <50x10^9/L (%)	7 (27)	4 (50)	2 (14)
Leukocytes x 10^9/L, median (range)	2.8 (1.4-97)	2.9 (0.5-33)	2.7 (1.5-9.8)
Neutrophils x 10^9/L, median (range)	0.8 (0.1-8.7)	1.0 (0.1-1.4)	1.1 (0.4-3)
Pts with neutrophils <1x10^9/L (%)	17 (65)	3 (37.5)	6 (43)
γ-globulin, g/L, median (range)	12 (7-19)	11 (9-14)	13 (9-21)
BM infiltration, median (range)	75 (15-95)	80 (50-90)	60 (10-90)
Hairy Cell Index, median (range)	0.5 (0.01-0.9)	0.5 (0.28-0.8)	0.4 (0.04-0.86)
Complete response (%)	5 (19)	6 (75)	12 (86)
Partial response (%)	15 (58)	2 (25)	2 (14)
No response (%)	6 (23)	0	0

BM: bone marrow HCL infiltration; group A: 2CdA in first-line therapy; group B: 2CdA in second-line therapy in patients resistant to or relapsed after IFN.

months (range 6-72), 6 of the 20 patients (30%) responsive to IFN still maintained their response, while 14 (70%) had relapsed. These included 3 of the 5 patients in CR (60%) and 11 of the 15 patients in PR (73%). Median PFS for these 20 patients was 19 months (Figure 1); no statistical differences were noted between the PFS of patients in CR and those in PR (p=0.3).

2CdA. All patients responded to 2CdA: overall, 18 (82%) obtained a CR and 4 (18 %) a PR. No differences were observed between 2CdA used as first- (group A) or second-line therapy (group B) (Table 1). The median nadir of circulating neutrophils was 0.4×10^9/L (0.1-1.4), and in eighteen patients (81 %, 8/8 of group A and 10/14 of group B) filgrastim 300 μg s.c. was given a median of 7 times (3-17). The number of circulating $CD4^+$ lymphocytes was 0.2×10^9/L (0.04-0.3) and 0.2×10^9/L (0.07-0.4×10^9/L) 2 and 12 months after therapy respectively. One patient in group A developed pneumonia 3 months after 2CdA but rapidly recovered with antibiotic therapy. Three patients (2 in group A and 1 in group B) experienced one episode of FUO. Hemoglobin and platelet reduction were mild and no extrahematological complications were observed. After a median follow-up of 14 months (range 4-37) only in 1 patient in group B showed disease progression 22 months after treatment (Figure 1).

In our series of 34 patients, with a median follow-up of 59 months (range 2-134), OS was 97% and only 1 person (a 48 year-old patient in complete remission) died of secondary acute non-lymphocytic leukemia 30 months after the end of 2 CdA and 44 months from diagnosis. No other secondary malignancies have been detected and, at present, all the other patients are alive.

Discussion

Our results underline the progress made in the treatment of HCL in these last two decades. Whether IFN[5] or purine analogues (namely 2CdA and deoxycoformycin) should be considered the first-line therapy for HCL is still debated, even though, looking at the results of most investiga-

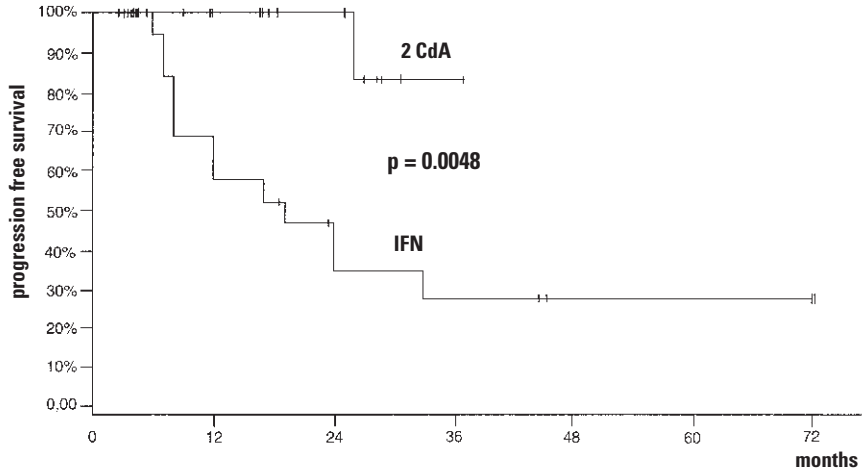

Figure 1. PFS curves of the patients treated with 2CdA and IFN-α. A significant advance was evidenced for 2CdA (p=0.0048).

to be the treatment of choice. In fact, compared to IFN, purine analogues substantially improve the rate of response (up to 80% CR) and produce durable remissions.[6-8] In our study DCF was excluded from the analysis due to the low number of patients treated with this drug.

The response rate observed in our cohort was similar to that reported in previous studies. In particular, treatment with 2CdA led to a higher CR rate and a statistical PFS advantage (p=0.0048) (Figure 1). Furthermore, the response was similar in both untreated and previously treated patients, confirming that 2CdA shows major activity even in patients resistant to IFN.

Since treatment with 2CdA is quite intensive and potentially more harmful than IFN, we also considered the toxic events associated with therapy. Both IFN and 2CdA proved to be safe. IFN caused mainly extrahematological toxicity, in particular a flu-like syndrome, as observed in other lymphoproliferative disorders,[9] while 2CdA induced predominantly hematological toxicity, in particular an initial neutropenia and a long-lasting lymphocytopenia. Nevertheless, major infective complications were observed in only one patient (a pneumonia 3 months after treatment). It should also be considered that long-term treatment with IFN involves a certain risk of autoimmune disorders.[10]

In conclusion, our experience confirms the high efficacy of 2CdA in the treatment of HCL. Since this agent also appears to be safe, especially if associated with growth factors, we believe that it should currently be preferred to IFN for the treatment of HCL. However, longer follow-up is required to establish the real impact of this drug on the OS of patients.

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