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HAIRY-CELL LEUKEMIA AND α-INTERFERON TREATMENT: LONG-TERM RESPONDERS

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ABSTRACT

Background and Objective. In the 1980s α-interferon (α-IFN) dramatically improved the management of hairy cell leukemia (HCL), producing normalization of hematologic parameters including the disappearance of circulating hairy cells in the majority of treated patients, within 6 months. The quality and durability of the response depended on the duration of α-IFN treatment; progression of the disease consistently followed discontinuation of α-IFN. In this report, we examine the characteristics of long-term responders from our series of 44 HCL patients treated with α-IFN.

Methods. We report follow-up data on 44 HCL patients who underwent α-IFN as first-line treatment between 1985 and 1990. The α-IFN dose was 3×10^6 U daily for 12-15 months, with 20 patients continuing to receive the same dose three times a week as maintenance treatment for an additional 6-12 months. Of the 44 patients, 8 achieved a CR, 28 a PR and 8 a MR, with an overall response rate of 82%. Thirty-eight (86%) of these patients showed disease progression and were retreated with α-IFN (2 pts), 2-chlorodeoxyadenosine (35 pts), or pentostatin (1 pt). So far, all 38 patients are alive and in good unmaintained second response, except for two patients who developed a second neoplasm.

Results. Six of the 8 first complete responders are alive and have not required further treatment after completing α-IFN. These long responders most often (5/6) presented a hairy cell index (HCI) < 0.50 at diagnosis; all 6 registered a significant reduction in bone marrow infiltration (HCI < 0.10) after induction therapy and underwent α-IFN maintenance treatment. These three parameters turned out to be statistically significant when the long-term responders were compared with the failure patients subset (p= 0.003 for HCI at diagnosis; p = 0.001 for HCI at the end of the induction phase; p = 0.003 for the maintenance phase). The median progression-free survival of these 6 long-term responders was 75 months (range, 62 to 78).

Interpretation and Conclusions. Overall, α-IFN represents an excellent palliative treatment for most HCL patients. A small subset of these patients could become long-term responders following first-line α-IFN therapy alone.

Hairy-cell leukemia (HCL) is a rare chronic lymphoproliferative disorder which generally occurs as the result of a monoclonal proliferation of B-lymphocytes, with irregular cytoplasmic projections, a characteristic tartrate-resistant acid phosphatase reaction, pancytopenia and splenomegaly.[1,2]

In the past, primary splenectomy was among the therapies most frequently recommended for this disease.[3,4] After 1984, following the initial studies of Quesada and coworkers,[5] dramatic results were reported with α-interferon (α-IFN).[6-11] In fact, α-IFN produced a favorable hematologic response in up to 90% of patients.[6-11] Although most responses are only partial and relapses requiring retreatment occur, survival rates have greatly improved and the estimated survival of patients treated with α-IFN is 85% to 90% at 5 years.[12,13] Recently, even better and more prolonged complete remission (CR) rates have been reported with the newer agents pentostatin (DCF) and 2-chlorodeoxyadenosine (2-CdA).[14-21]

Since a significant number of HCL patients treated with α-IFN have been followed for more than 5 years, it is now possible to report extended follow-up information on HCL patients treated with α-IFN to evaluate its long-term efficacy and late side effects. In this report, we examine the characteristics of long-term responders from our series of 44 HCL patients treated with α-IFN. We endeavored to identify any pretreatment or in-treatment factors that might predict good response and outcome, and to identify what percentage of HCL patients is cured utilizing α-IFN.

Patients and Methods

We retrospectively examined data from the 44 HCL patients (37 males and 7 females) with a median age of 54 years (range, 33 to 76 years) who completed at least 12 months of α-IFN treatment between April 1985 and September 1990. Table 1

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summarizes the clinical characteristics of these patients. Criteria for inclusion in the study were: i) HCL diagnosis on the basis of the morphologic, immunologic, and bone marrow features; 2) 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 1 to 24 months.

The patients were treated with human lymphoblastoid α-IFN (Wellferon), kindly provided by Wellcome (Mountain View, CA, USA), and all of them received 3×10^6 units (3 MU) a day, self-administered subcutaneously for 12-15 months. Twenty of these patients, according to a previous 1:1 randomization at diagnosis, continued to receive the same dose three times per week as maintenance treatment for an additional 6-12 months. While receiving α-IFN, patient underwent complete blood counts with differential and chemistry panels monthly; bone marrow studies were done initially and every 6 months thereafter to assess cellularity, HC infiltration and hairy-cell index (HCI), defined as % cellularity × % HC/100.

Response criteria

Complete response (CR) was defined as the absence of HC in peripheral blood and bone marrow, disappearance of splenomegaly (when present), recovery of peripheral blood counts (hemoglobin > 12 g/dL, platelets > 100×10^9/L, and neutrophils > 1.5×10^9/L). Partial response (PR) was defined as a HC decrease in the bone marrow of more than 50%, accompanied by restoration of peripheral blood counts (as defined for CR) for at least 3 months. Minor response (MR) was designated as a restoration of at least one of the peripheral blood parameters (as defined above). Progression of disease (PD) was defined as a decrease in hemoglobin to less than 10 g/dL without clinical signs of bleeding, a decrease in the absolute neutrophil count to less than 1.5×10^9/L in three consecutive counts, or a decrease in platelets to less than 100×10^9/L.

Statistical analysis

The duration of response to α-IFN was defined as the period of time from the achievement of the response to relapse or death. This time period, denoted as progression-free survival, was determined, as was overall survival, according to the method of Kaplan and Meier.[22]

Results

Of the 44 patients, 8 (18%) achieved a CR, 28 (64%) a PR and 8 (18%) a MR, with an overall response rate (CR+PR) of 82%. A higher CR rate was observed in patients with a low HCI (< 0.50): 5/8 (62.5%) versus 3/8 (37.5%) in the group with a HCI > 0.50 at diagnosis (p= 0.05) (data already published).[11]

Median overall survival for the 44 patients was 88 months, with a range of 63-126 months. Thirty-

Table 1. Clinical characteristics of the 44 HCL patients who entered the α-IFN study.

No. patients	44
Sex M/F	37/7
Age (years)	
median	54
range	33-76
Previous splenectomy	5
Splenomegaly	29
No splenomegaly	10
α-IFN maintenance Yes/No	20/24

eight of the 44 (86%) patients showed disease progression, which was characterized by leukopenia and thrombocytopenia in 26 patients and thrombocytopenia alone in 9 patients. Among the relapsed/progressed patients, the event occurred at a median of 14 months (range, 4 to 42) after the end of treatment. PD took place in 29/30 (97%) patients with a HCI > 0.50 at diagnosis, whereas in the group of 14 patients presenting a HCI < 0.50 before α-IFN treatment, we observed a PD rate of 64% (9/14) (p= 0.003). PD patients all underwent α-IFN retreatment and/or DCF or 2-CdA protocols. Currently, all these patients are in second CR or PR after α-IFN reinduction (2 patients), 2-CdA (35 patients), or DCF (1 patient). Concerning these retreated patients, all of them obtained a second response which has persisted since the end of treatment and is unmaintained, except for 2 patients who developed a second neoplasm and died: one of a brain tumor (15 months after starting α-IFN) and one of a pancreatic carcinoma (24 months after starting α-IFN).

Of the 8 complete responders after first induction with α-IFN, only 6 continue to be in first CR. Four are males and 2 females, with a median age of 57 years (range, 50 to 69). Four of these patients presented splenomegaly at diagnosis. Their clinical, hematologic and histologic characteristics are illus-

Table 2. Clinical and histologic characteristics of the 6 long-responder HCL patients.

Pts	*Sex/Age*	*Hematologic parameters* *Hb**	*Neutr.**	*Plts**	*Splenomegaly (size)°*	*Cellularity/ infiltration*	*HCI at diagnosis*	*α-IFN duration (months)*	*HCI post α-IFN*	*Duration of response*	*Cellularity/ infiltration*	*Current HCI*
1	F/52	10.4	0.5	179	no	0.50×0.90	0.45	18	0.02	60	0.40×0.035	0.015
2	M/59	12.6	0.4	59	yes (5 cm)	0.65×0.90	0.58	18	0.05	72	0.35×0.04	0.015
3	M/48	10.2	1.2	117	yes (2 cm)	0.10×0.80	0.08	18	0.03	75	0.40×0.035	0.015
4	M/44	10.3	0.4	19	no	0.50×0.90	0.45	24	0.02	78	0.20×0.10	0.020
5	M/64	10.4	0.8	69	yes (8 cm)	0.50×0.90	0.45	20	0.02	75	0.20×0.10	0.020
6	F/50	9.2	2.5	51	yes (10 cm)	0.60×0.80	0.48	18	0.05	62	0.20×0.10	0.020

**Hb (g/dL), neutrophils (x 10^9/L), platelets (x 10^9/L); °from the costal margin.*

trated in Table 2. At diagnosis all but one of these 6 patients displayed a HCI < 0.50.

All 6 long-term responders obtained a significant reduction of bone marrow hairy-cell infiltration (HCI < 0.10) at the end of α-IFN induction therapy (6/18 among those with HCI < 0.10 versus 0/26 among those with > 0.10; p= 0.001). All these patients underwent α-IFN maintenance treatment after the induction phase (6/20 with maintenance versus 0/24 without maintenance; p = 0.003). The total duration of α-IFN treatment was 18 months for 4 of the patients, and 20 and 24 months, respectively, for the other two. The median progression-free survival of these long responders is 75 months (range, 62 to 78). Their median survival from the initiation of α-IFN treatment is 93 months (range, 78 to 102).

As regards their peripheral blood parameters, all six patients currently display a CR picture without circulating hairy cells, and none of them has splenomegaly. Bone marrow biopsies were reevaluated at least 5 years after the completion of α-IFN treatment and in all 6 cases the HCI was less than 0.025, with residual hairy-cell infiltration ranging between 3% and 5%.

Discussion

Since it was first defined by Bouroncle *et al.*,[1] HCL has been shown to have a particularly variable natural outcome. In fact, some patients can follow the *watch and wait* approach for several years without needing any therapy, while others rapidly develop a hematologic crisis that requires urgent treatment.

The introduction of α-IFN markedly changed the management of HCL but only now, after a long follow-up, it is possible to know how much this therapy affects long-term survival and clarify some of the clinical and histologic characteristics of long-term responders to α-IFN.

This study confirms and extends the results reported by other investigators[23-26] concerning the percentage (10-15%) of long-term responders among HCL patients who undergo first-line α-IFN treatment. In fact, of our 44 evaluable HCL patients, only 6 (14%) have not required retreatment for more than 5 years after the completion of first-line α-IFN therapy. In addition, two specific histologic factors characterized these long-term responders: HCI < 0.50 at diagnosis (5/6 patients) (p= 0.003) and HCI < 0.10 at the end of α-IFN therapy (6/6 patients) (p= 0.001). Another parameter shared by these 6 patients was prolonged therapy with α-IFN (at least 18 months of treatment) (p= 0.003).

The question of late side effects was represented by the presence of 2 secondary malignancies (2/44, 4.5%), but these data are insufficient to examine whether the secondary neoplasms could be related to HCL or to α-IFN treatment. It should be noted that our incidence data are lower than those observed by other authors.[27,28]

In conclusion, α-IFN may represent an excellent palliative treatment for HCL patients. It is possible that an identifiable subset of patients (10-15%) may exist for whom no other treatment but α-IFN induction and maintenance is necessary. Patients in this subset seem to be characterized by low hairy-cell infiltration in the bone marrow at diagnosis, a significant reduction of bone marrow hairy-cell infiltration after the induction phase, and a benefit from maintenance therapy. In addition, most of the patients who progressed after α-IFN obtained a CR with DCF or 2-CdA. In fact, in the last few years the introduction of purine analogs (DCF and 2-CdA) has resulted in CR rate of more than 80%.[14-21]

On the basis of these data, it would be possible to utilize α-IFN as induction therapy in those patients with low bone marrow infiltration and cellularity (HCI < 0.50) at diagnosis since they could probably obtain a very good and prolonged response without myelosuppression toxicity, immunosuppression, or the infective complications associated with purine analogs.[29] In fact, these side effects are extremely important in HCL patients using DCF or 2-CdA. On the other hand, for patients with a very high HCI (> 0.50) the first-line treatment might be 2-CdA or DCF, considering the statistically significant role of the bone marrow tumor burden and the possibility of achieving a higher CR rate and a more durable response with these purine analogs.

In very few cases of HCL, α-IFN may cause autoimmune hemolytic anemia.[30] Current data are insufficient to assess the risk of a second neoplasm. It will be very important to continue the follow-up of these patients with the aim of extrapolating any correlation between α-IFN therapy and the risk of late neoplastic sequelae.

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