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-chlorodeoxy-adenosine (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). 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 HCL at diagnosis; p = 0.001 for HCL 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. ©1997, Ferrata Storti Foundation

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.3-5 After 1984, following the initial studies of Quesada and coworkers,6 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.9-11 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
summarizes the clinical characteristics of these patients. Criteria for inclusion in the study were: 1) 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 (HCl), 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 with or 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.21

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 HCl (< 0.50): 5/8 (62.5%) versus 3/8 (37.5%) in the group with a HCl > 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-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 HCl > 0.50 at diagnosis, whereas in the group of 14 patients presenting a HCl < 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 induction (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 illustrative.
treated in Table 2. At diagnosis all but one of these 6 patients displayed a HCl < 0.50.

All 6 long-term responders obtained a significant reduction of bone marrow hairy-cell infiltration (HCl < 0.10) at the end of α-IFN induction therapy (6/18 among those with HCl < 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 HCl 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., 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 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: HCl < 0.50 at diagnosis (5/6 patients) (p = 0.003) and HCl < 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.

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%.

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 (HCl < 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. 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 HCl (> 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. 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.

References

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