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Hairy Cell Leukaemia: The Role of Alpha Interferon

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Hairy cell leukaemia (HCL) is a chronic progressive disease of predominantly middle-aged men. Alpha interferon has been shown to induce significant responses in HCL patients. With interferon treatment the platelet count normalizes first, followed by the haemoglobin and neutrophil counts. The number of hairy cells in the bone marrow decreases and granulocytic, erythroid and megakaryocytic cells increase. Interferon is well tolerated with the most common side effect being a flu-like syndrome. A number of HCL patients will develop neutralizing antibodies and in these cases the chemotherapeutic agents pentostatin and 2-chlorodeoxyadenosine should be considered. Preliminary results with these agents are promising and further trials are ongoing to confirm their clinical promise.
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INTRODUCTION

HAIRY CELL LEUKAEMIA (HCL) is a rare chronic lymphoproliferative disorder, first described in 1958 by Bouroncle *et al.* as leukaemic reticuloendotheliosis [1]. The disease has a chronic progressive course characterized by splenomegaly, pancytopenia, and recurrent infections. The prognosis of HCL compares favourably with that of other lymphoproliferative disorders, due to the slow, chronic course of the disease. Despite this, prior to the introduction of alpha interferon therapy many patients developed serious complications which were associated with significant morbidity and mortality. The introduction of alpha interferon in the management of HCL significantly altered the prognosis of patients, decreasing the frequency of complications and improving overall survival. HCL was the first malignancy where a biological response modifier was shown to have significant activity. In this review we summarize the experience with the use of alpha interferon in the treatment of this leukaemia, and attempt to define the precise role of this agent in the treatment of the disease with the currently available data.

CLINICAL FEATURES OF HAIRY CELL LEUKAEMIA

HCL is sometimes difficult to diagnose, despite the advances in laboratory haematology and immunology. The disease usually affects middle-aged white men, and the male to female ratio is approximately 5:1 [2]. HCL patients usually present with symptoms secondary to the pancytopenia, such as weakness and fatigue due to anaemia, bleeding due to thrombocytopenia, and bacterial or opportunistic infections due to neutropenia or the underlying severe immunodeficiency. Splenic pain due to marked splenomegaly occurs in 25% of patients and is sometimes the presenting symptom. Occasionally, HCL is found in asymptomatic patients who undergo routine evaluation [2-4].

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Approximately 20% of the patients present with the leukaemic phase of the disease with a high white blood cell count (>10,000/μL) and more than 50% circulating hairy cells [5]. The diagnosis is usually based on the bone marrow biopsy, where there is usually diffuse infiltration of the bone marrow by hairy cells and staining for tartrate resistant acid phosphatase is almost always positive. When a diagnostic dilemma exists, immunohistochemical studies of the bone marrow specimens with the monoclonal antibodies CD11c, CD22 and CD25 usually establish the diagnosis [6, 7].

Not all patients with HCL require treatment. Approximately 10% of affected patients will have a prolonged course, up to 10 years, without requiring any form of therapy [2, 3]. Most patients, however, will require some form of treatment during the course of their disease. The most common reason to initiate treatment is neutropenia with or without associated infections and thrombocytopenia. A significant percentage of patients require treatment for symptomatic splenomegaly [8].

SPLENECTOMY

Splenectomy was the treatment of choice for HCL patients for 25 years prior to the introduction of alpha interferon therapy [1]. It still should be considered as an initial treatment option for patients who present with significant splenomegaly and minimal bone marrow involvement [9-11]. The spleen size does not seem to correlate with response [5], and the most important prognostic factor for haematological recovery after splenectomy seems to be the degree of bone marrow cellularity [11]. Almost half of the patients who have a haematological response after splenectomy will eventually require systemic treatment [4], with a median interval period of 8.3 months [8, 12].

ALPHA INTERFERON

Mechanism of action

Since the first report of successful treatment of HCL patients with alpha interferon in 1984 [13], the approach to the management of the disease has changed dramatically. The long-term survival of HCL patients has increased significantly, and the morbidity from the manifestations of the disease has been markedly reduced.

Alpha interferons are a group of glycoproteins with similar

biological effects and a common receptor on a variety of normal and malignant cells. These proteins have multiple activities including antiviral, anti-proliferative and immunomodulatory effects [14-16]. The initial trials of alpha interferon in HCL utilized partially purified alpha interferon and subsequent studies utilized recombinant human interferon alfa-2a or alfa-2b.

The mechanism of action of alpha interferon in HCL remains controversial. *In vitro* data support both a direct effect on hairy cells and an indirect effect by activation of non-specific anti-neoplastic immune mechanisms. Hairy cells have been shown to express much higher numbers of alpha interferon receptors than other neoplastic cells or normal B-lymphocytes [17]. Alpha interferon has been shown to have a direct biochemical effect on hairy cells *in vivo*, with a marked induction of an 80,000 dalton protein [18]. In addition, alpha interferon induces the expression of class II human lymphocyte antigens (HLA) on hairy cells, which could make them more susceptible to the lytic action of cytotoxic T-cells [19, 20]. Alpha interferon was also found to induce *in vitro* differentiation of multilineage lympho-myeloid stem cells in patients with HCL, suggesting that its action may be at the level of an early precursor of hairy cells [21]. Finally, interruption of autocrine loops for the growth of hairy cells has also been suggested. Alpha interferon, but not gamma interferon, inhibits B-cell growth factor- [22] or tumour necrosis factor- [23] induced hairy cell proliferation. Despite the diversity of the proposed mechanisms for its action and the inability to define them precisely, alpha interferon has an impressive *in vivo* inhibitory effect on hairy cell growth.

Clinical data

Alpha interferon is currently approved by the Food and Drug Administration (FDA) for use in the treatment of patients with HCL. The first report of the effectiveness of this agent was published in 1984 by Quesada *et al.* [13]. In this trial, partially purified alpha interferon was used at a dose of 3 million units (MU) intramuscularly to treat seven patients with HCL. Three patients obtained complete remissions with normalization of all haematological parameters and a complete pathological response in the bone marrow. The other four patients obtained partial remissions with normalization of the haematological parameters and greater than 50% reduction in the percentage of hairy cells infiltrating the bone marrow. Subsequent to this, other investigators confirmed the significant activity of alpha interferon in HCL, by using recombinant interferon alfa-2b or alfa-2a preparations (Table 1) [24-30]. The overall response rate is 80-90% with approximately 5% of the patients obtaining complete responses, 70-80% obtaining partial responses with normalization of all three cell lines and an associated decrease in bone marrow involvement, and 5-10% obtaining minor responses with improvement of at least one blood count. The variability in the reported cases of complete responses probably reflects the differences in the dose and schedule of alpha interferon used. The results from all these studies show that alpha interferon is active in both splenectomized and previously untreated patients. However, patients with a previous history of splenectomy seem to have a better overall response to alpha interferon therapy than non-splenectomized patients [24].

There are no accurate predictive values for response to interferon therapy. Ratain *et al.* [31] showed that the median duration of response in responders to alpha interferon is approximately 25 months. In this study the two best predictive values for duration of response were the neutrophil alkaline phosphatase (NAP) score and the degree of residual hairy cell infiltrate in the bone marrow at the completion of therapy. Patients with a NAP ≥ 30 and more than 30% hairy cell infiltrate in the bone marrow had a median duration of response of 12.4 months. In contrast to this, patients with a NAP < 30 had a median duration of response of 30.4 months. Finally patients with a NAP ≥ 30%, but less than 30% infiltration of the bone marrow had an intermediate prognosis with a disease-free interval of 23.5 months [29]. The usual dose schedule for interferon alfa-2b is 2 MU/m² three times a week administered subcutaneously for 12 months. When smaller doses were used for the same duration of treatment the results were clearly inferior [32]. The usual dose of interferon alfa-2a is 3 MU/m² daily for 6 months. Regarding the duration of treatment, Golomb *et al.* [33] randomized 90 responders to 12 months of interferon alfa-2b therapy to receive either no treatment or an additional 6 months of interferon therapy. The prolongation of treatment to 18 months seemed to delay the relapse rate while the treatment continued, but did not extend the length of remission duration after the discontinuation of treatment [33]. Therefore the recommended duration of treatment is 12 months, but longer treatment periods can be considered if there are no significant side effects and the patient tolerates the treatment well. It is also possible that chronic maintenance treatment with lower doses may be useful in the maintenance of remission induced with standard doses, but there are no data to support this hypothesis as yet.

During treatment with alpha interferon a rapid response is seen first in the platelet count, which usually normalizes within 2 months. The haemoglobin and neutrophil counts increase more gradually and usually normalize after 1-8 months of treatment. It is not uncommon to see transient myelosuppression during the first 1-2 months of therapy, and this should not lead to discontinuation of treatment [34]. Patients in the leukaemic phase of the disease who present with very high white blood cell counts also have a rapid response to interferon treatment with normalization of the white blood cell count by 8 weeks. In the bone marrow, the number of hairy

Table 1. Results of clinical trials with interferon in hairy cell leukaemia

Study	Interferon type	Dose schedule	Evaluable patients (≥ 4 months of IFN)	CR %	PR %	MR %
Golomb *et al.* [24]	Alfa-2b	2 MU/m² t.i.w.	128	4	74	7
Ratain *et al.* [31]	Alfa-2b	2 MU/m² t.i.w.	68	13	62	16
Quesada *et al.* [29]	Alfa-2a	3 MU q.d. x 4-6 mths then t.i.w.	30	30	57	0
Foon *et al.* [28]	Alfa-2a	3 MU q.d. x 6 mths mths then t.i.w.	12	8	83	8
Lauria *et al.* [30]	Alpha partially purified	3 MU q.d. until CR, then t.i.w.	23	30	48	22

CR = complete response, PR = partial response; MR = moderate response;

cells decreases and the numbers of granulocytic, erythroid, and megakaryocytic cells usually increase within 3-6 months after initiation of therapy [35]. The severe deficiency of natural killer cell activity that these patients have is usually corrected within 3-6 months of therapy [36].

Patients who may benefit best by initial treatment with interferon are those with a very hypercellular bone marrow (cellularity > 85%), patients in the leukaemic phase of their disease, and patients with tissue involvement, such as large lymphadenopathy or bony lesions. Patients with serious underlying immunodeficiency who present with opportunistic infections without neutropenia are also good candidates for initial induction with interferon. In general, interferon treatment should be given as the first line of treatment to patients with an indication for systemic treatment. In patients who relapse after remission induction with interferon, the decision whether to retreat them with interferon or to use one of the other active agents in the treatment of HCL (pentostatin, 2-chlorodeoxyadenosine (2-CDA)) should be individualized. The length of the remission and the quality of the previous response to interferon are factors that should influence the decision [37]. There are no data at this time to compare retreatment with interferon to treatment with chemotherapeutic agents in first relapse, but it has been shown that most of the relapsing patients can obtain a second remission on retreatment with interferon [31].

Toxicities

Interferon treatment, at the doses used in HCL, is usually well tolerated and discontinuation of the therapy because of toxicity is rare. The most common side effect is the development of a flu-like syndrome during the first week of treatment that resolves over the next 2-4 weeks. Other side effects include asymptomatic hepatitis, abnormal taste, paraesthesias, transient skin rashes and gastrointestinal symptoms [24-30]. Rarely, patients may develop central nervous system toxicity or severe peripheral neuropathy necessitating discontinuation of treatment. As mentioned earlier in the text, transient myelosuppression is very common, and this can be explained by the direct effect of interferon on bone marrow progenitors [16].

Development of antibodies against interferon

Resistance to interferon therapy associated with the development of neutralizing antibodies has been reported recently [38]. In this study, antibodies to human recombinant interferon alfa-2a developed in 31 out of 51 patients treated. Sixteen of these patients had neutralizing antibodies to interferon alfa-2a, and clinical resistance to therapy developed in six of them. These neutralizing antibodies were found as early as 4 months and as late as 12 months during the treatment period. Other investigators have also reported development of antibodies during treatment with interferon alfa-2a [39, 40]. In contrast, development of neutralizing antibodies during treatment with interferon alfa-2b for HCL has been reported only in one case [41] and it does not seem to pose a significant problem in the vast majority of patients. It is unclear why patients with HCL treated with interferon alfa-2b infrequently develop antibodies, as neutralizing antibodies to interferon alfa-2b have been reported in approximately 30% of patients with chronic myelogenous leukaemia receiving treatment with this agent [42]. In patients who receive interferon alfa-2a and develop clinical resistance associated with neutralizing antibodies, a change of therapy to pentostatin or 2-deoxychloroadenosine is indicated. Theoretically, partially purified alpha interferon may also be effective in these patients, but there are not enough clinical data to support its use.

CHEMOTHERAPEUTIC AGENTS

In the pre-interferon era, attempts to treat HCL patients with single agents, such as chlorambucil, or combination chemotherapy regimens were of limited success. Recently, the introduction of pentostatin and 2-CDA in clinical trials has given chemotherapy an important role in the management of the disease (Table 2). These two agents are still experimental and the experience with 2-CDA is very limited, but both seem to be very promising.

Table 2. Active agents in the treatment of hairy cell leukaemia

Drug	Mechanism of action	Complete remissions	Partial remissions	Effect on the immune system	Adverse effects
Alpha interferon*	Unknown	< 5%	80%	Immunostimulatory	Fever Flu-like syndrome Central nervous system toxicity Gastrointestinal toxicity Chronic fatigue syndrome Myelosuppression Development of antibodies
Pentostatin	ADA inhibitor	60-90%	10-40%	Immunosuppressive	Nausea Vomiting Skin rash Myelosuppression Renal toxicity
2-Chlorodeoxyadenosine†	ADA-resistant purine analogue	90%	10%	Unknown	Myelosuppression Fever

*FDA approved. †Based on a single study.

The experience with pentostatin is more extensive, and large clinical trials have confirmed its efficacy in the treatment of HCL. Spiers *et al.* [43] first reported induction of complete remissions in two patients with HCL in 1984, using pentostatin at a dose of 5 mg/m² two-three times per week for 15-16 weeks. Subsequent to this, larger clinical trials also confirmed the significant activity of this agent, even at lower and less toxic doses [44-46]. The drug has activity both in previously untreated patients and in interferon-resistant patients. The overall number of complete remissions reported is 60-90% and of partial remissions 10-40%. So far, with a median follow-up of 2 years, the reported complete remissions have been durable in contrast to the ones obtained with alpha interferon. These data suggest that pentostatin may be curative in some patients, although longer follow-up is necessary. The toxicities of pentostatin include nausea, vomiting, conjunctivitis, skin rash, myelosuppression and transient renal insufficiency. The major problem with the use of pentostatin, however, seems to be immunosuppression [47]. The drug is not yet approved by the FDA, but can be obtained from the National Cancer Institute by the special exemption mechanism for patients who are resistant to interferon [48].

Recently, Piro *et al.* [49] reported their experience with 2-CDA in 12 patients with HCL. This drug is a recently developed adenosine deaminase-resistant purine analogue, with cytotoxic activity that is independent of cell division [50]. The results of this trial were impressive. Eleven out of 12 patients obtained complete remissions after a single infusion of 2-CDA. The remissions have been lasting with the longest follow-up being 3.8 years. The toxicities of the drug were fever and mild myelosuppression [48]. Based on the data from this trial, it seems that this agent will eventually have a major role in the treatment of patients with HCL. Larger studies are now underway to confirm its activity.

FUTURE ROLE OF ALPHA INTERFERON IN HAIRY CELL LEUKAEMIA

It is difficult to know whether interferon will have a role in the treatment of HCL in the future with the availability of pentostatin and 2-CDA. Interferon has been shown to be a safe treatment that can control the disease for long periods of time, but it is not curative. It is possible that some of the patients who were treated with pentostatin have been cured of their disease, but the short follow-up does not permit such a conclusion. Furthermore, pentostatin is immunosuppressive, while interferon is immunostimulatory, and this may be of clinical significance in patients who have severe underlying cellular immune deficiency. A randomized cancer and leukaemia group B trial comparing interferon with pentostatin as initial treatment has just been completed but the data are not yet available. Until longer follow-up of the pentostatin-treated patients is available, that clearly establishes the durability of responses and excludes significant long-term toxicities, interferon should be used as initial treatment when systemic therapy is needed. In patients resistant to interferon, or who relapse after interferon, pentostatin treatment may be given either by the special exception mechanism or by participation in ongoing multicentre trials. 2-CDA seems to be more promising than both interferon and pentostatin. The drug had only moderate or no toxicity, and induced lasting complete remissions by single infusions. However, the results are still preliminary as they are based on a single clinical trial in a small number of patients. Again, as with pentostatin, 2-CDA treatment should be given only in well-controlled trials. Time will show if this drug will maintain its initial clinical promise.

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DISCUSSION AFTER PLATANIAS

Freund (Germany): Dr Ratain, you have clearly demonstrated that most of the patients taken off interferon will relapse. Although relapsers still, in general, have a good prognosis, and so the overall survival of your patients is very good, you have reported that three patients died from relapse. What would be your general recommendation against that background? Is it really wise to take patients off interferon?

Ratain (U.S.A.): I think it is a very reasonable option to keep patients on interferon, but one must balance the toxicity of the drug with the risk of stopping it. If a patient can be managed in a careful manner off interferon, i.e., they can be watched because they are in close proximity to the physician or can be managed by telephone, then I think it is reasonable to stop. The failures we have had on stopping interferon have mostly been patients that were not easy to manage - that is, they lived a long way from our clinic. We now have ongoing a single-arm pilot study of maintenance interferon at one-tenth the standard dose for an additional 2 years to assess whether this will affect the median time to relapse of 2 years. Our assumption is that we should see half our patients relapsing by the end of that maintenance period, if the maintenance therapy has no effect. This study was started about a year ago so it is really too premature to make any comments.

Question from the floor: If you have very early responses, in less than 3 or 4 months, do you continue treatment until 12 months or do you shorten it?

Ratain (U.S.A.): We continue until 12 months, but I don't think anybody knows the best duration of treatment. We know that 18 months does not decrease the tumour burden below that which can be achieved with 12 months. Again, it is possible that shorter treatment, or higher doses of interferon might be better.

Schwarzmeier (Austria): In which cases do you still perform splenectomy?

Ratain (U.S.A.): In patients whose bone marrow involvement does not exceed 85%, we still consider that splenectomy is a very reasonable option. We tell the patients that the use of interferon in non-splenectomized cases usually results in some degree of residual hypersplenism, i.e., the response in the platelet count, neutrophils and haemoglobin may not be as good. The choice really depends on the patient, as there is great difference between having one operation and having 1-3 years of injections 3 times a week.

Question from the floor: If you achieve a response to interferon treatment in a non-splenectomized patient, would you then do a splenectomy?

Ratain (U.S.A.): We have no experience with that, although I believe Dr Pangalis' group has looked at it. I would anticipate that one would see an improvement in the blood count after removing the spleen, so I think that is a reasonable option. In general, we really prefer splenectomy as initial treatment in our patients so we don't have a lot of experience in non-splenectomized patients.