megakaryocytopoiesis by alpha interferon [8]. Alpha interferon induced a decrease in the megakaryocyte density and size, suggesting a selective influence on megakaryocytes at various stages of maturation [9]. This is in accordance with a phase I study involving daily administrations of interferon in which a significant reduction in platelet count was observed in several patients within 2 weeks [10].

The effects of alpha, beta and gamma interferon alone or in combination were studied in ET using the mixed colony formation assay. Bone marrow precursors were cultured in the presence of each type of interferon, and the results indicated that alpha interferon would be the best candidate for reducing the megakaryocyte precursors [11].

Alpha interferon has been shown in a number of studies to be a useful agent for ET [3, 4, 12-14]. In the present study the efficacy of alpha interferon (nine responses out of 13 patients) has been confirmed with rapid reductions in platelet levels.

Following the initial reduction in platelet count, maintenance therapy with interferon is required in most patients. In patients who complete the initial course of therapy, excellent therapeutic effects can be achieved on long-term treatment. In our patients, the main problems have been poor tolerance of the induction regimen and leucopenia. Sometimes it is difficult to treat an asymptomatic patient with a drug that has definite clinical side effects, even if they are mild. Moreover, a recent Spanish study [15] has shown a survival curve for ET patients similar to that of a normal age-matched population. This supports the view that therapy for asymptomatic ET should not be based only on a high platelet count.

In conclusion, interferon alfa-2b is a useful agent in the treatment of ET. Nevertheless, the frequent side effects observed in our study and the usual good prognosis make it advisable to reduce the dose of interferon alfa-2b, and to treat only those patients with significant signs and symptoms associated with very high platelet counts.

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Alpha Interferon in Chronic Lymphocytic Leukaemia

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The role of alpha interferon in patients with chronic lymphocytic leukaemia (CLL) has yet to be well established. In studies carried out to date, a significantly higher response rate has been observed in previously untreated patients compared to those who have received prior chemotherapy. Patients with early-stage CLL also respond better than patients with advanced disease. Responses to alpha interferon are transient and complete responses are rare. It is not yet known whether alpha interferon can induce clonal remission, and response is usually measured in terms of the reduction in peripheral blood lymphocyte levels. In one study, a normalization of immunoglobulin levels was observed, and in another there was an increase in the absolute

number of granulocytes. Further studies are needed to investigate the role of combined therapy with alpha interferon and cytotoxic agents or other cytokines, and to assess the ability of alpha interferon to prolong response duration after remission induction with chemotherapy. Toxicity is tolerable when alpha interferon is given in a low dose (e.g., 2 million units (MU)/m² three times a week) and low doses have been shown to be as effective as high doses in CLL patients.

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INTRODUCTION

CHRONIC LYMPHOCYTIC leukaemia (CLL) is a disorder characterized by the progressive accumulation of B-lymphocytes, and by a heterogeneous clinical course. Treatment is unsatisfactory and, in most instances, has a merely palliative effect [1]. Therefore, the search for new forms of treatment for CLL is warranted.

Interferons are a group of naturally occurring substances which are being actively investigated in the therapy of different haematological neoplasms. It is usually considered that alpha interferon has only limited activity in CLL [2-6], although this concept is based on results achieved in previously treated patients, and patients with advanced disease, a setting where treatment failures are the rule. Results obtained in previously untreated patients in early clinical stage have been more encouraging [7-10]. Herein, we briefly review the role of alpha interferon in CLL therapy.

CLINICAL TRIALS WITH ALPHA INTERFERON IN CLL

Reported clinical trials of alpha interferon in CLL are summarized in Table 1.

Treatment schedules

Dose. The optimal dose of alpha interferon for CLL therapy is not well established. In the trials published so far, the dose used has been highly variable. Thus, in initial studies, alpha interferon was given in a flat dose of 10 million units (MU) or more [2, 3, 5]. In other trials, the dose has been adjusted to the body surface area (2 MU/m² to 50 MU/m²), [2, 7] with reductions or increments of the initial dose (from 10% to 75%) according to toxicity [2] or response [3, 4, 8]. In general, doses higher than 10 MU are poorly tolerated, necessitating dose modifications. In more recent reports, a flat dose ranging from 1.5 MU to 9 MU (most frequently 2 or 3 MU) has been used [4, 6, 8-10].

Frequency of administration.

Alpha interferon is usually given three times a week (t.i.w.), with only two studies using a daily dose schedule [4, 6]. Whether a daily schedule is more effective than intermittent administration has not been determined.

Route of administration.

Alpha interferon has most commonly been given intramuscularly [2, 3, 5, 7, 9]. In some trials, however, alpha interferon has been administered subcutaneously [10], this latter route having the advantage of allowing self-administration of the product by the patients.

Treatment duration.

The duration of initial treatment has ranged from 1 to 4 months [3, 6], with alpha interferon usually being continued if some degree of response is observed [8]. Again, the optimal duration of treatment is not well established. As with hairy cell leukaemia and low-grade non-Hodgkin's lymphomas, however, treatment should probably be maintained for no less than 1 year if a response is observed after an initial treatment period of 2 to 3 months.

Therapeutic results

As shown in Table 1, previous therapy has an important influence on response to alpha interferon. Whereas in previously untreated patients the number of responses is high (52/72 or 73%), the response rate is much lower (4/40 or 10%) ($P < 0.001$) in patients who have received prior therapy. In one trial in previously untreated patients, immunoglobulin levels normalized after alpha interferon treatment [10]. In another [7], an increase in the absolute number of granulocytes was observed. In all cases, however, clinical responses are minor and transient. A reduction in the number of lymphocytes in peripheral blood is the most consistent finding. It is noteworthy that among more than 100 patients treated so far, only a "clinical" complete response (CR) has been observed. Although Foon *et al.* [2] observed disease progression in some of their patients treated with alpha interferon, the relationship between alpha interferon and disease progression is unclear since all their patients had advanced disease at the time of recruitment to the study. The relationship between tumour burden and response is also difficult to establish since, in most reports, patients' clinical stage is not specified. It appears, however, that the less advanced the clinical stage, the higher the response rate. In this regard, the results obtained at our institution in previously untreated patients with early stage disease are of some interest [7]. Ten patients with early B-CLL (seven in Rai's stage 0, three in stage I) were treated with alpha interferon (2 MU/m² intramuscularly t.i.w. for a minimum of 14 weeks) to assess its effectiveness. In all cases, a definite, although transient, reduction in the absolute number of peripheral blood lymphocytes was observed. No CRs were achieved. In eight patients, an increase in the absolute number of granulocytes was detected. Treatment was remarkably well tolerated. These results, suggesting that low doses of alpha interferon are active in CLL, have been confirmed by others [8-10] (see Table 1).

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Table 1. Clinical trials with alpha interferon in CLL patients: summary of results

Author (year)	No cases/stage	Previous therapy	Dose/Schedule	Response
Foon *et al.* (1985) [2]	19 II = 6, III + IV = 13	Yes	50 MU/m² or 5 MU/m² i.m. t.i.w.; 3 months	2 (11.1%) PR 5 (27.8%) SD 11 (61.1%) PD
Horning *et al* (1985) [6]	10	1 No 9 Yes	1 MU, 3 MU or 9 MU i.m. daily 30 days	10 (100%) SD
Schuloff *et al.* (1985) [5]	12 0 = 1, I = 3, II = 4, IV = 4	4 No 8 Yes	20 MU/m² i.m. t.i.w.; 8w	2 (16.7%) PR 10 (83.3%) PD
Talpaz *et al* (1987) [4]	10 0 = 2, I = 1, II = 6 III = 1	6 No 4 Yes	3 MU i.m. every day increased to 9 MU	3 (30.0%) PR 4 (40.0%) MR 3 (30.0%) SD
Overall	51	11 No 40 Yes		7 (14.0%) PR 4 (8.0%) MR 18 (36.0%) SD 21 (42.0%) PD
O'Connell *et al.* (1986) [3]	4	No	12 MU/m² i.m. t.i.w.; 8w increase if NR to 25 MU/m²	1 (25.0%) PR 2 (50.0%) SD 1 (25.0%) PD
Rozman *et al.* (1988) [7]	10 0 = 7, I = 3	No	2 MU/m² i.m. t.i.w.; 14w	10 (100%) PR
Boussiotis and Pangalis (1988) [8]	26 A =26	No	1.5 MU, t.i.w. 3 months foll. by three diff. schedules	1 (3.8%) CR 9 (34.6%) PHR 7 (26.9%) MR 8 (30.8%) SD 1 (3.8%) PD
Ziegler-Heitbrock *et al.* (1989) [10]	9 A0 = 4, AI = 3, AII = 2	No	5 MU s.c. t.i.w.	5 (55.5%) PR 2 (22.2%) MR 2 (22.2%) SD
Molica *et al.* (1990) [9]	11 A0 = 8, BI = 1, BII = 1, CIV = 1	No	3 MU i.m. t.i.w.; 14w	6 (55.5%) PR 4 (44.4%) MR 1 (9.1%) SD
Overall	60	No		1 (1.7%) CR 31 (51.7%) PR 13 (21.7%) MR 13 (21.7%) SD 2 (3.3%) PD
Overall previously treated	40			5 (10.2%) R 16 (41.0%) SD 19 (48.7%) PD
Overall previously untreated	71			52 (73.2%) R 15 (21.1%) SD 4 (5.6%) PD

w = week; t.i.w. = 3 days per week; i.m. = intramuscular; s.c. = subcutaneous; CR = complete response (no evidence of disease); PR = partial response (reduction ≥50% of all measurable lesions); PHR = partial haematological response (reduction ≥50% of blood lymphocytes); MR = minor response (reduction between 25%-50%); SD = stable disease; PD = progressive disease: R = response; NR = no response.

Toxicity

The side effects observed in patients with CLL do not differ from those reported in patients with other haematological malignancies treated with alpha interferon. The majority of patients experience a flu-like syndrome, which is particularly evident during the first weeks of therapy. The severity of this flu-like syndrome is variable but tends to be higher in patients treated with high doses of alpha interferon [2, 3, 5] although, in one study, no relationship was found between the dose of alpha interferon and the severity and duration of side effects [6]. Fatigue can be marked and persistent [4, 5]. Apart from these rather common effects, a number of less frequent side effects have been reported, including reduction in Karnofsky performance score [2], weight loss [4, 5], muscular pain [4], gastrointestinal symptoms (including nausea, vomiting, and diarrhoea) [3-5], intercurrent and severe bacterial or viral infections [2, 6, 8], pneumonitis [6], allergic reactions [3], hair loss [10], and neurological manifestations, such as ataxia and confusion [3] or worsening of previous depression [10]. Haematological toxicity has also been noticed in some trials. This includes anaemia, thrombocytopenia or granulocytopenia, which are usually moderate, and occasionally mediated by immune mechanisms [6, 8, 9].

Conclusions

From the review of these reports, it can be concluded that:

1) Alpha interferon is not effective when given to previously treated CLL patients and patients with advanced disease.

2) Doses of alpha interferon higher than 10 MU are poorly tolerated.

3) Alpha interferon is active when given to previously untreated CLL patients in early clinical stage.
4) Responses are transient.
5) Complete remissions (CR) are rarely, if ever, achieved.

FUTURE TRENDS

In the future, several new treatment strategies and studies merit consideration:

1) The effect of alpha interferon combined with other cytokines or cytotoxic agents.
2) The role of alpha interferon in prolonging responses achieved with conventional chemotherapy.
3) The capacity of alpha interferon to induce "clonal" remissions in CLL patients achieving a "clinical" CR.
4) The impact of alpha interferon on the immune status of CLL patients.

Regarding the use of cytotoxic agents in combination with alpha interferon, preliminary results in 11 patients treated with alpha interferon at our institution, after tumour mass reduction with chlorambucil, suggest that this approach may produce better results than alpha interferon alone (unpublished results). In other trials, the effectiveness of alkylating agents given simultaneously with alpha interferon, rather than sequentially, is being investigated. The combined use of different cytokines (e.g., alpha interferon plus interleukin-2) is also of interest.

The impact of alpha interferon on response duration should also be studied. There is evidence from studies in multiple myeloma and non-Hodgkin's lymphomas that alkylating agents and alpha interferon have a synergistic effect, and that alpha interferon prolongs responses achieved with chemotherapy [11, 12]. Similar results in CLL would not be surprising.

As previously mentioned, CRs are rarely, if ever, obtained with conventional chemotherapy in CLL. In the majority of patients who achieve a CR (clinical and haematological), it is possible to demonstrate persistence of the abnormal leukaemic clone if appropriate studies (e.g., cell markers; Ig rearrangement analysis) are carried out. The potential of alpha interferon for inducing "clonal" CR in such cases deserves investigation.

Finally, different immune disturbances exist in CLL (e.g., hypogammaglobulinaemia, imbalance in T-cell subsets, decreased natural killer cell [NK] function). The effect of alpha interferon on such parameters has not been clearly determined although, in one report, immunoglobulin levels returned to normal after alpha interferon treatment [10]. On the other hand, alpha interferon has been shown to increase NK activity. In a recent study from our group, it was found that initial therapy with chlorambucil did not modify decreased NK activity in patients with early CLL but that alpha interferon given subsequently did so (unpublished results). Whether the immune modifications induced by alpha interferon have a significant clinical impact is not known and should be investigated further.

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DISCUSSION AFTER MONTSERRAT

Chisesi (Italy): Dr Montserrat, at what stage do you decide to treat CLL patients?

Montserrat (Spain): At the present time, probably the best decision for patients in Stage A - and particularly those in Stage A0 - is not to treat them at all. I think there is no proof that treatment in this particular group of patients has any advantage, particularly for those patients described as having smouldering CLL by the French group and ourselves. My aim was to investigate a new treatment approach in patients with very low tumour burden. This is in an investigational setting and not in everyday practice.

Question from the floor: Did you see an effect on the immunoglobulin levels in your patients?

Montserrat (Spain): No, we didn't. I am aware that a paper from Ziegler-Heitbrock *et al* published in *Blood* [10] a few months ago stated that in some patients with hypogammaglobulinaemia, one of the effects of interferon was to return the immunoglobulin levels to normal, but none of our patients had hypogammoglobulinaemia so we could not look at that particular point.

Freund (Germany): Dr Montserrat, it was a little bit disappointing that, in your first study, you were able to lower lymphocyte counts very quickly but they then stayed on a plateau. If the rationale is to eliminate minimal residual disease, this approach seems to have problems. Do you plan further studies using combinations of cytotoxic agents and interferon?

Montserrat (Spain): This would be a very interesting approach - for example, to try fludarabine with alpha interferon. One approach should be to see whether interferon is capable of prolonging responses obtained with chemotherapy, because one of the problems that we have in CLL is that responses are usually transient, whatever treatment is given.

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