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Randomized Study of Chlorambucil (CB) Compared to Interferon (Alfa-2b) Combined with CB in Low-Grade Non-Hodgkin's Lymphoma: An interim report of a randomized study

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Alpha interferon has shown initial promise in the treatment of low-grade non-Hodgkin's lymphoma (NHL), especially with the nodular form of the disease. The present study enrolled 70 NHL patients who received either chlorambucil (CB; 10 mg/day) or CB plus interferon alfa-2b (5 million units (MU)/m² subcutaneously three times a week). Among 63 evaluable patients, similar response rates (62.1% and 64.7% respectively) were recorded for the treatment arms. In patients receiving no maintenance therapy, those who received interferon alfa-2b during the induction phase showed a favourable trend in terms of incidence of relapse compared to those who had received chlorambucil alone. During maintenance therapy with interferon alfa-2b, no significant differences in the occurrence of relapse have yet been seen compared to patients on no maintenance therapy. A longer observation period is needed to make a definitive conclusion about the usefulness of interferon maintenance therapy and to evaluate further the effects of the combined schedule of chlorambucil and interferon induction on the duration of remission.
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INTRODUCTION

ALPHA INTERFERON has been shown to be an active agent in haematological malignancies, especially hairy cell leukaemia (HCL) and low-grade non-Hodgkin's lymphoma (NHL) [1]. So-called 'favourable prognosis' or 'low-grade' NHL include all those with a follicular pattern except large-cell lymphomas. The natural history of these neoplasms, and their response to available therapy varies according to histological type. Nodular (follicular) non large-cell lymphomas may follow an almost benign clinical course and some authors have advocated minimal therapeutic intervention.

Therapeutic options

At present, the majority of patients with stage III and IV follicular lymphoma are treated conservatively. The observation that selected patients without symptoms and with 'minimal' disease may be treated expectantly in the first instance without compromising their survival has led many investigators to adopt a policy of close follow up with institution of therapy only with the emergence of symptoms or progressive disease.

When treatment is indicated, cyclophosphamide or chlorambucil, with or without prednisone, are the most widely used drugs yielding response rates of about 75%, with the median duration of remission being between 1 and 2 years [2].

Treatment of NHL with alpha interferon has shown greater promise with the nodular than with the diffuse form of the disease [3]. The therapeutic activity of interferon in lymphoma remains poorly defined. It has been demonstrated that the long-term administration of low-dose interferon will produce a clinical response in 30-40% of patients with low-grade NHL, with minimal toxicity [4]. Combination of interferon with conventional cytotoxic agents has been reported in many experimental models and subsequently in several clinical trials in order to assess the synergism and toxicity [5-7].

Although the initial studies have been encouraging, the place of interferon in the current management of indolent NHL has not yet been established; furthermore, it is unclear whether the use of interferon in combination with other drugs is more effective and, finally, whether maintenance with interferon would prolong the duration of remission obtained in these patients. The results of a phase II study conducted in our department from 1985 to 1986 demonstrated a response rate of 60% to an interferon combination (better than previous experience with alpha interferon alone) and mild toxicity [8]. In order to verify the above findings, the following randomized study comparing chlorambucil with a combination of chlorambucil and interferon alfa-2b has been performed.

PATIENTS AND METHODS

By July 1989, 70 patients with low-grade NHL were enrolled in the study. The characteristics of patients are shown in Table 1. Treatment consisted of chlorambucil at a dosage of 10 mg/day for 3 weeks (Arm A) or chlorambucil at a dosage of

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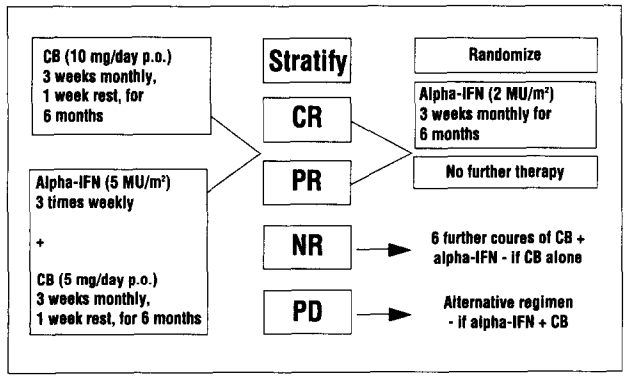
Table 1. Chlorambucil versus chlorambucil + interferon in low-grade NHL: cooperative randomized study. Clinical characteristics of patients

		Patients *n* (%)	
Enrolled patients		70	
Evaluable patients		63	(90)
Sex			
Male		36	(57.1)
Female		27	(42.9)
Age (years)			
Mean	61		
Median	62		
Range	28-84		
Histology (W.F.)			
B		36	(57.1)
C		27	(42.9)
Stage			
III		8	(12.7)
IV		55	(87.3)
Systemic symptoms		24	(38.1)
Performance status			
0 (90-100)		41	(65.1)
1 (70-80)		21	(33.3)
2 (50-60)		1	(1.6)

5 mg/day plus recombinant interferon alfa-2b 5 million units (MU)/m² subcutaneously three times a week (t.i.w.) for 3 weeks (Arm B), for a total of six cycles with a 1-week rest between each cycle (Fig. 1). Patients achieving complete or partial response during induction therapy were further randomized to receive interferon maintenance or no maintenance therapy.



CR = complete response; PR = partial response; NR = no response; PD = progression of disease.

Fig. 1. Guidelines of the proposed randomized study comparing chlorambucil (CB) versus CB plus interferon alfa-2b as initial therapy for low-grade NHL.

Response criteria

Patients were evaluated for clinical response every 4 weeks and clinically restaged at the completion of the therapy. The response was evaluated as follows: complete remission was defined as disappearance of all evidence of tumour for a minimum of 2 months; partial remission was defined as over 50% reduction of all measurable tumour for a minimum of 1 month, with concurrent amelioration of performance status (PS) according to Karnofsky score; no response was judged as no improvement of PS and either no reduction of lymphadenopathy or progression of disease when increase of adenopathies were observed.

RESULTS

Sixty-three patients were considered for response to therapy and seven patients were excluded either for refusing treatment (two patients) or lost from follow-up (two patients) or major toxicity (three patients). Twenty nine patients were evaluable in Arm A (chlorambucil) and 34 patients in Arm B (chlorambucil + interferon). Similar response rates of about 62 and 65% were registered in the two arms, respectively (Table 2). Toxicity was

Table 2. Chlorambucil (CB) versus CB + interferon in NHL: outcome of therapy

First randomization						
	Arm A (CB) Patients *n*	(%)		Arm B (CB + interferon) Patients *n*	(%)	
CR	10	(34.5)	}(62.1)	8	(23.5)	}(64.7)
PR	8	(27.6)		14	(41.2)	
SD	3	(10.3)		5	(14.7)	
PD	8	(27.6)		7	(20.6)	
Total	29			34		

CR = complete response; PR = partial response; SD = stable disease; PD = progression of disease.

quite acceptable in most cases, but slightly greater in Arm B. Thus far, there is no statistically significant difference in overall survival between the two groups (Fig. 2). There is a suggestion

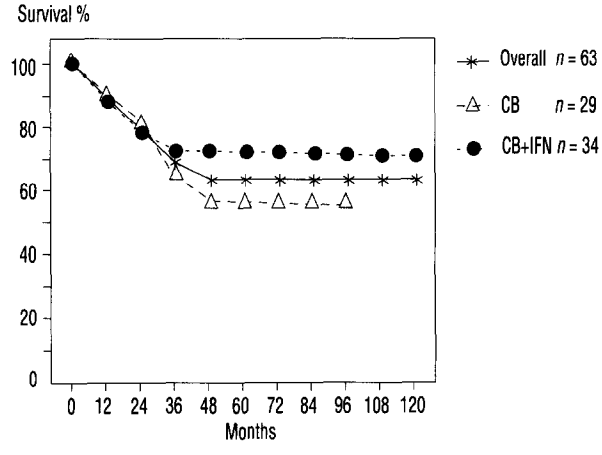


Fig. 2. CB versus CB + interferon study in low-grade NHL. Overall survival.

that maintenance therapy with alpha interferon is active in reducing or delaying the occurrence of relapse (Fig. 3). Furthermore, considering patients who had or had not received

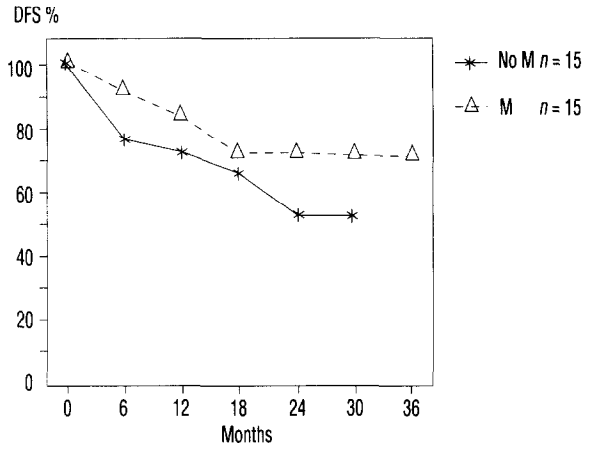


Fig. 3. DFS according to second randomization.

interferon during the induction treatment a lower relapse rate has been observed in patients who did receive interferon.

DISCUSSION

The chlorambucil plus interferon regimen used in our study demonstrated that this schedule is effective and non-toxic in patients with NHL, even if given in combination and for a long time. The response rate does not seem to be increased on the combination as compared to chlorambucil alone, an observation that may be related to the relatively low number of patients enrolled in the two arms or to the schedule.

In patients who responded, the clinical effect was slow but progressive and toxicity did not increase with cumulative doses. In contrast, disease progression was very rapid in non-responders and increasing the dose did not improve efficacy.

In our study, the use of low-dose recombinant interferon alfa-2b in combination with chlorambucil demonstrated a good response rate which was comparable or superior to higher doses, without toxicity. However, the duration of response and the efficacy of the maintenance regimen have yet to be established, and it is of major importance that we determine whether interferon maintenance therapy will prolong the interval of remission or reduce the incidence of relapse. Although initial results are favourable for patients on the maintenance regimen, a longer observation time is required to evaluate this aspect of the study.

An important additional question raised by our results is whether the action of interferon during induction therapy might influence the response, preventing or delaying disease recurrence. The apparent advantage for patients who received interferon during induction therapy versus patients who did not seems to confirm the usefulness of interferon in this respect. Nevertheless, because of the long median survival of these patients, a more prolonged observation period is needed to make a definitive conclusion about the usefulness of interferon maintenance therapy and to confirm the efficacy of the combined schedule of chlorambucil plus interferon according to duration of response.

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