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Interferon Alfa-2b in Addition to Chlorambucil in the Treatment of Follicular Lymphoma: Preliminary Results of a Randomized Trial in Progress

Christopher G.A. Price, Ama Z.S. Rohatiner, William Steward, David Deakin, Nigel Bailey, Andrew Norton, George Blackledge, Derek Crowther and T. Andrew Lister

One hundred and twenty four patients with follicular lymphoma (32 with Stage III and 92 with Stage IV disease) have been randomized to receive chlorambucil alone or chlorambucil plus interferon alfa-2b. Responding patients are then randomized to receive either interferon alfa-2b maintenance therapy for up to 12 months or no further treatment. One hundred and eight patients are evaluable for response, the remainder are still receiving initial therapy. Clinical remission (complete or good partial remission) was achieved in 42/59 (71%) patients receiving chlorambucil alone and in 27/49 (55%) patients receiving the combination (P = NS). Preliminary analysis of remission duration shows a trend in favour of those patients receiving interferon throughout (P = 0.02). There is no significant difference between the groups in terms of survival, at a median follow up of 2.5 years. Interferon-associated toxicity was minor in most patients but led to discontinuation of therapy in six cases. Larger trials with longer follow-up periods are needed to confirm the beneficial role of interferon in the treatment of follicular lymphoma.
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THE CLINICAL COURSE of follicular lymphoma characteristically follows a remitting, relapsing pattern, with repeated responsiveness to alkylating agents [1]. Chlorambucil (CB) induces remission, usually incomplete in the majority of cases, in a schedule with relatively minor morbidity [2]. Interferon, given alone in low doses over a period of months, also causes regression of disease, again with generally acceptable toxicity [3-6]. These results, combined with data from animal models of leukaemia and lymphoma [7, 8] and extrapolation from human (solid cancer) xenograft studies [9] which suggested synergy between alkylating agents and alpha interferon, prompted this investigation of the combination of chlorambucil and interferon for the treatment of follicular lymphoma. A feasibility study was undertaken, and it was concluded that the combination could be given with reasonable tolerance [10]. Modest encouragement was taken from the better response rate in heavily pretreated patients than had previously been achieved with chlorambucil alone. Thus a randomized clinical trial was designed to determine whether the combination might alter the clinical course described above. In addition to a comparison between CB and CB plus interferon alfa-2b as initial therapy, a further randomization was included to test the proposition that prolongation of interferon therapy might be advantageous, as had been suggested from its use in treatment of both chronic myeloid leukaemia and hairy cell leukaemia [11, 12]. Preliminary results are reported below for this collaborative trial which is still in progress.

Correspondence to: T. A. Lister.
T. A. Lister is at the ICRF Department of Medical Oncology, St Bartholomew's Hospital, London EC1, U.K. C.G.A. Price and A.Z.S. Rohatiner are at the ICRF Department of Medical Oncology, St Bartholomew's Hospital, London EC1, U.K. W. Steward and D. Crowther are at the CRC Department of Medical Oncology, Christie Hospital and Holt Radium Institute, Manchester, U.K. D. Deakin is at the Department of Radiotherapy, Christie Hospital and Holt Radium Institute, Manchester, U.K. N. Bailey and G. Blackledge are at the CRC West Midland Clinical Trials Unit, Queen Elizabeth Hospital, Birmingham, U.K. A. Norton is at the Department of Histopathology, St Bartholomew's Hospital, London EC1, U.K.

MATERIALS AND METHODS

One hundred and twenty-four adults aged 26-81 years (median 52 years), with stage III (n = 32) and stage IV (n = 92) follicular lymphomas, whose clinical presentation was deemed to warrant therapy have been entered on this trial. One hundred and eight form the basis of the analysis, with 16 still receiving initial therapy.

Treatment

The study design and regimen are shown in Figure 1, the second randomization being stratified according to response to first therapy. Patients at St Bartholomew's Hospital received maintenance interferon for 1 year after the second randomization, while patients from the Christie Hospital and the Queen Elizabeth received it only to the completion of 1 year from presentation (i.e., 7 months). Both approaches have yielded the same results to date. Interferon was administered subcutaneously.

Treatment modification

Treatment was discontinued for 2 weeks in patients with treatment-related cytopenia (neutrophil count <1 x 10^9/L, platelet count <100 x 10^9/L) and was restarted in full dosage after recovery of the count. Persistent or recurrent cytopenia

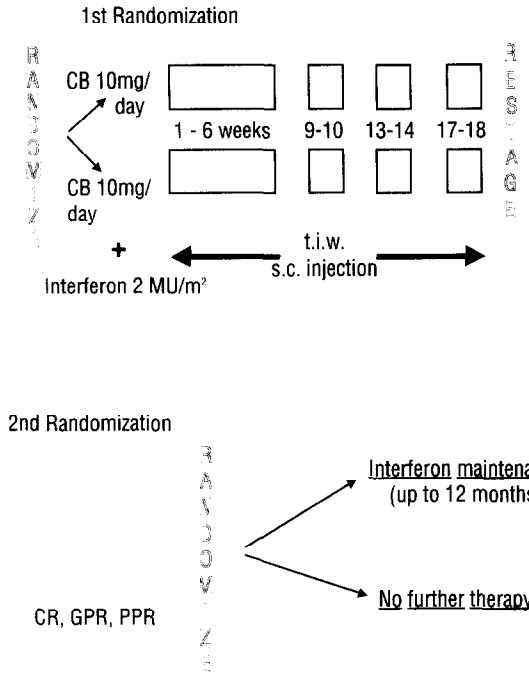

Fig. 1. Study design. CB = chlorambucil, IFN = interferon alfa-2b, CR = complete remission, GPR = good partial remission, PPR = poor partial remission.

provoked a 50% reduction in chlorambucil dose or discontinuation of therapy. Persistent intolerable subjective side effects of interferon were managed by 50% dose reduction or cessation of that agent alone.

During the trial period the policy was changed for patients in whom only a poor partial remission (PPR) was achieved, such that some of the latter were not entered into the second part of this trial but went on to receive more intensive chemotherapy in an attempt to achieve complete remission (CR). Patients in whom the response is classified as PPR are therefore considered separately, and not considered in terms of duration of remission.

Assessment of response

Response to therapy was first assessed at 1 month after completion of CB or CB plus interferon alfa-2b.

Definition of response

Response was defined as either complete remission (CR; no evidence of residual disease); good partial remission (GPR; clinical complete response with minimal residual abnormality on radiographic or bone marrow examination); poor partial remission (PPR; reduction >50% in any measurable lesion associated with improvement in non-measurable involvement, i.e., less than GPR or failure to respond [fail]). Duration of remission was recorded from the time of reassessment at 5 months; relapse was defined as recurrent or progressive disease and was confirmed histologically.

Statistical methods

Survival and remission duration curves were plotted according to the method of Kaplan and Meier [13], and the log rank method was used for significance of differences in distributions.

RESULTS

Response to initial therapy (Table 1)

Clinical remission was achieved in 71% of patients receiving chlorambucil alone, and in 55% of those receiving the combination (P = N.S.).

Table 1. Interferon alfa-2b and chlorambucil for follicular lymphoma. Response to initial therapy

	CB	CB + interferon alfa-2b
CR + GPR + PR	51/59 (86%)	38/49 (78%)
CR + GPR	42/59 (71%)	27/49 (55%)
CR	15/59 (25%)	8/49 (16%)

Duration of remission

The duration of remission for patients entering CR and GPR according to the first and second randomizations is shown in Figure 2, with an advantage in favour of those patients receiving interferon throughout (P = 0.02). Ten patients did not enter the second part of the trial because: 1) the response to initial therapy was PPR (see above); 2) it was the patient's wish; or 3) it was the physician's choice.

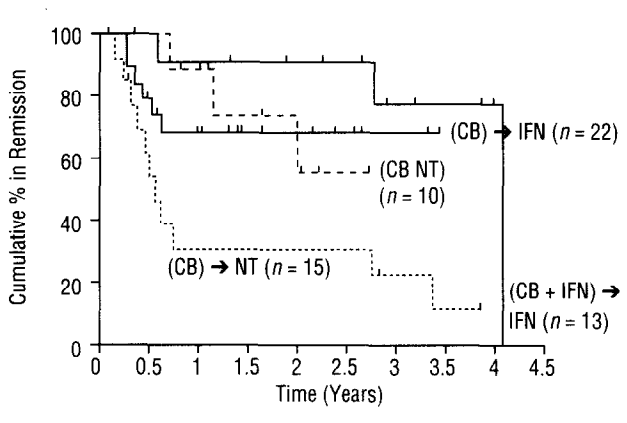

Fig. 2. Duration of remission according to treatment. CB = chlorambucil, IFN = interferon alfa-2b, NT = no treatment.

Survival

Ninety-six patients are still alive, while 28 have died, at a median follow up of 2.5 years. No significant differences for the different treatment groups have emerged.

Toxicity

Most patients initially experienced subjective systemic symptoms from interferon alfa-2b as previously described [14]; these were insufficient to interfere with daily activities in the majority but led to discontinuance of the drug in six cases (8%). One patient developed haemolytic anaemia within 2 weeks of starting interferon alfa-2b (as 'maintenance'). Interferon alfa-2b

was also possibly associated with the exacerbation of angina in one patient, and an epileptiform seizure in another. Three patients suffered skin rashes attributable to CB. Thirty one/49 (62% of patients receiving CB + interferon alfa-2b) had periods of cytopenia sufficient for their treatment to be delayed compared to 9/59 (16%) who received CB alone ($P < 0.01$).

DISCUSSION

It is encouraging that this preliminary analysis indicates a potential role for interferon in the treatment of follicular lymphoma. However, enthusiasm for the results must be greatly tempered by the very short follow up, the small numbers of patients, and the knowledge that previous clinical trials which have shown an advantage in terms of duration of remission for either intensification of initial therapy [15] or maintenance [16] have failed to translate this into prolonged survival. The large multicentre trials presently in progress will undoubtedly clarify this issue. Perhaps another question might be, for how long should the interferon be given?

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