A randomized controlled trial to evaluate the role of interferon as initial and maintenance therapy in patients with follicular lymphoma

A Rohatiner1, J Radford2, D Deakin3, H Earl3, SB Love4, O Price1, A Wilson1 and TA Lister1

1ICRF Medical Oncology Unit, St. Bartholomew’s Hospital, West Smithfield, London EC1A 7BE; 2Christie CRC Research Centre, Christie Hospital, Wilmslow Road, Manchester M20 9BX; 3Birmingham Oncology Centre, Queen Elizabeth Hospital, Dudley Road, Birmingham B18 7QH; 4ICRF Medical Statistics Group, Institute of Health Sciences, Old Road, Headington, Oxford OX3 7LF

Summary The purpose of this study was to evaluate the role of interferon as initial and maintenance therapy in patients with newly diagnosed follicular lymphoma. Between 1984 and 1994, 204 patients with newly diagnosed Stage III or Stage IV follicular lymphoma were randomized to receive either, Chlorambucil (CB): 10 mg daily for 6 weeks, followed by a 2-week interval, with 3 subsequent 2-week treatment periods at the same dose, separated by 2-week intervals, or, CB given concurrently with interferon (IFN). IFN was given at a dose of 3 \times 10^6 units thrice weekly, subcutaneously, throughout the 18-week treatment period. Responding patients were subsequently randomized to receive maintenance IFN at the dose and schedule described above, or to expectant management. The overall response rate was 161/204 (78%), complete remission being achieved in 24% of patients. Neither the addition of IFN to the initial treatment, nor the use of maintenance IFN influenced response rate, remission duration or survival. This study was undertaken to determine whether IFN, given in combination with, and then subsequent to, CB would alter the clinical course of patients with follicular lymphoma. Disappointingly, this objective was not achieved, no advantage having been demonstrated for the addition of IFN. © 2001 Cancer Research Campaign

Keywords: interferon; initial therapy; maintenance; follicular lymphoma

PATIENTS AND METHODS

Patients

231 newly diagnosed patients with Stage III or IV follicular lymphoma whose clinical characteristics at presentation are shown in Table 1 were entered into the study between October 1984 and October 1994. Patients were treated at 3 main centres: the Christie Hospital, Manchester (104 patients), St. Bartholomew’s Hospital, London (60 patients), and Queen Elizabeth Hospital, Birmingham (22 patients). 18 patients were referred from other hospitals. 204 patients form the basis of this analysis, 27 having been excluded for the following reasons: incorrect histology on review: 14, incorrect stage on review: 10, previous treatment: 3.

Stage had been determined from the history, accompanied by clinical examination, computed axial tomography (CT) of the chest, abdomen and pelvis, and unilateral iliac crest bone marrow aspirate and biopsy. Liver involvement was diagnosed on the basis of confirmation of defects seen on CT scanning by ultrasonography.

Treatment

The overall strategy is outlined in Figure 1. After informed consent had been obtained, patients were randomly allocated to receive either, CB: 10 mg daily for 6 weeks, followed by a 2-week interval, with 3 subsequent 2-week treatment periods at the same dose, separated by 2-week intervals or the latter given concurrently with IFN. Patients randomized to CB + IFN, received the latter at a dose of 3 \times 10^6 units thrice weekly, subcutaneously,
concurrently throughout the 18-week treatment period. 100 patients were randomized to CB alone, 104 to the combination.

CB or CB + IFN was discontinued for 2 weeks in the first instance in patients with treatment-induced neutropenia (neutrophils < 1 x 10^9 1^-1) or thrombocytopenia (platelets < 100 x 10^9 1^-1) and restarted at full dosage upon recovery. Persistent or recurrent cytopenia led to a 50% reduction in the CB dose, or ultimately to discontinuation of therapy. Intolerable subjective side-effects attributable to IFN were managed in the first instance by a 50% dose reduction and if they persisted, by discontinuation.

For the first 2 years of the study, patients with responding or ‘stable’ disease were randomized to maintenance IFN or to no further treatment, following stratification for response. Subsequently, randomization was limited to patients in whom a complete or ‘good partial response’ (GPR) was achieved (see below), it being considered more appropriate to administer alternative treatment to those in whom less than GPR was achieved. Maintenance IFN (at the same dose and schedule as used initially) was given for one year, except at the Christie Hospital, where it was stopped after 6 months. Outcome (in terms of remission duration and survival) was the same, irrespective of the length of time for which maintenance IFN was given, the results have therefore been combined.

108 of 126 eligible patients were randomized, 18 were not, for the following reasons: error; 6, prior IFN toxicity; 5. 4 patients declined randomization, and 1 developed recurrent lymphoma within 4 weeks of finishing initial treatment. In 2 patients, second randomization was considered inappropriate (due to persistent neutropenia, and the development of angina respectively). The number of patients actually receiving CB or the combination, followed by IFN or no further treatment is shown in Table 2.

Patients were seen every 2 weeks whilst receiving Chlorambucil and monthly whilst receiving maintenance IFN (or being managed expectantly if randomized to this arm of the study). Subsequently, all patients were seen at 3 monthly intervals. Management following recurrence was determined by the circumstances: in younger patients, further chemotherapy was given to induce second remission with a view to proceeding to myeloablative therapy supported by autologous bone marrow transplantation (Rohatiner et al, 1994).

**Post-treatment evaluation and definition of response**

Formal re-evaluation comprising clinical examination, CT scanning and repeat bone marrow biopsy (if previously positive) was undertaken one month after completion of initial treatment (unless there was a clinical indication to do so earlier).

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 CT scans or bone marrow trephine; poor partial remission (PPR): >50% reduction in any measurable lesion associated with improvement in nonmeasurable involvement, i.e. less than GPR; failure to respond: anything less than PPR.

**Statistical analyses**

In the original study protocol, it was considered necessary to accrue 200 patients in order to demonstrate a difference in remission duration of 35–40%. The following factors were tested for possible influence on response, remission duration and survival: gender, age, presence of B symptoms, hepatosplenomegaly, stage, anaemia (Hb < 11.5 g), abnormalities of liver function, performance status and treatment with IFN.

**Randomization balance**

The study was randomized to achieve balance between the treatment groups for both known and unknown prognostic factors. Each variable (other than age) was therefore considered against the randomization code. Balance for age (the only continuous variable) was considered by looking at the median for each randomization group.
**Predicting response**

Variables were considered one at a time by calculating Fisher’s exact test on tables of the variable vs response. Variables found to be significant at $P < 0.1$ were put into a logistic model, together with liver function (to adjust for balance). Only liver function and variables with $P < 0.05$ were retained. Results of the logistic regression analysis are given in terms of Odds ratios, an Odds ratio of 2 for Hb (normal vs low) being interpreted as a patient with a normal Hb having twice the chance of response as a patient with a low Hb, all other prognostic factors being the same.

**Remission duration analysis**

Remission duration was defined as the time from date of response to date of recurrence and was considered only for those patients in whom CR or GPR was achieved. Univariate analysis was performed by means of the Log-rank test and survival plots drawn using the Kaplan–Meier method (Kaplan and Meier, 1958). All variables significant at $P < 0.1$ in the log-rank analysis were put into a backward stepwise Cox Regression model (Kaplan and Meier, 1958). The proportional hazards model assumption was assessed by means of log minus log hazard plots. The Cox results are expressed in terms of hazard ratios, a hazard ratio of 2 for anaemia again being interpreted as a patient with anaemia having twice the risk of recurrence as a patient with a higher Hb, all other prognostic factors being the same.

**Survival**

Survival was defined as the time from first randomization until death, or last follow-up. Analyses were performed using the same methods as described above for remission duration.

**RESULTS**

**Response** (Table 3)

The overall response rate was 78% (161/204), CR being achieved in 24% of patients (49/204). For patients who received CB as initial treatment, the overall response rate was 84% (84/100), for those receiving CB + IFN it was 74% (77/104). However, the CR + GPR rate was higher in patients receiving Chlorambucil alone (70/100, 70% vs 56/104, 54%, $P = 0.02$).

Univariate analysis using the Fisher Exact test showed gender, B symptoms, performance status, liver function, anaemia, age and treatment to predict for response. The final logistic (multivariate) model on 183 patients with complete data is shown in Table 4. ‘Forcing’ the first randomization code into this model, the odds ratio for CB + IFN vs CB alone is 0.5 (with a 95% confidence interval of 0.2–1.1, $P = 0.04$). The addition of IFN to CB as initial treatment did not improve response rate.

| Variable   | Coding | OR (95% CI) | P  
|------------|--------|-------------|-----
| Gender     | F vs M | 2.3 (1.0–5.2) | 0.04
| Liver function | poor vs normal | 0.4 (0.2–0.95) | 0.04
| Performance status | change of one level | 0.5 (0.3–0.9) | 0.03
| Age        | 10-year difference | 0.7 (0.5–1.0) | 0.05

**Remission duration**

Since for most of the duration of the study, only patients in whom CR or GPR was achieved (the majority) continued in the study (the rest receiving alternative therapy), only this sub-group has been included in the analysis of remission duration. With a median follow-up of 8.5 years, the median remission duration is 3.8 years (Figure 2); 88 patients have developed recurrent lymphoma. 2 patients died in remission, the latter have therefore been censored.

On univariate analysis, lymph node enlargement, anaemia and the addition of IFN were significant prognostic factors (liver function being included for adjustment). When liver function was included in the Cox model, no variable was found to be significant (Table 5). ‘Forcing’ liver function and the addition of IFN into the Cox model (on 116 patients with 78 recurrences) gives a hazard ratio for CB + IFN vs CB of 0.7 (95% confidence interval 0.4–1.1, $P = 0.09$). On multivariate analysis, adjusting for potentially unbalanced factors and for other prognostic factors, the addition of IFN to CB as the initial treatment did not significantly influence remission duration.

**Survival**

The median survival was 8.5 years (Figure 2); 93 patients have died, 70 as a consequence of disease progression, 10 of the latter dying of complications of further treatment. 12 patients died of

| Variable   | Coding | HR (95% CI) | P value
|------------|--------|-------------|------
| Liver function | poor vs normal | 1.4 (0.8–2.2) | 0.2
| 1st. randomization | CB + IFN vs CB | 0.76 (0.4–1.1) | 0.09

HR = hazard ratio; CI = confidence interval.
causes unrelated to lymphoma or its treatment (myocardial infarction 4, other malignancies 4, cerebrovascular accident 2, haemorrhage 1, pulmonary embolism 1).

On univariate analysis, B symptoms, liver function, performance status, splenomegaly, anaemia and age were significant prognostic factors. The final Cox model results (on 183 patients with 82 deaths) are shown in Table 6. ‘Forcing’ the addition of IFN into this model gives a hazard ratio for CB + IFN vs CB of 1.00, (95% confidence interval 0.64–1.6, \( P = 1.0 \)). On multivariate analysis, adjusting for potentially unbalanced factors and for other prognostic factors, the addition of IFN to CB as initial treatment did not influence survival.

**Effect of maintenance IFN on remission duration**

Complete or good partial remission was achieved in 126 patients who were therefore eligible for second randomization. 108/126 were actually randomized, 60 to receive maintenance IFN, 48 to no further treatment. Overall, 74 patients developed recurrent lymphoma; 2 who died without recurrence are censored.

On univariate analysis, none of the factors considered were significant. On multivariate analysis, ‘forcing’ the use of maintenance IFN into a Cox model gives a hazard ratio (for no further treatment vs IFN maintenance) of 1.4, (95% confidence interval 0.9–2.2, \( P = 0.1 \)). The use of maintenance IFN did not therefore significantly influence remission duration. Considering the 4 possible treatment combinations resulting from the first and second randomizations, (analysing 108 patients with 74 recurrences in a Cox model) no sequence of treatments was significantly better in terms of remission duration than CB followed by no further treatment. These results are shown in full in Table 7 and in Figure 3.

**Effect of maintenance IFN on survival**

Once more, only patients in whom CR or GPR was achieved were considered. Survival from second randomization was analysed using the same methods as described above for analysis of survival from the time of diagnosis. On univariate analysis, liver function, anaemia and age were found to be significant prognostic factors. On multivariate analysis, (using the Cox model on 108 patients with 34 deaths), only age gave a hazard ratio of 1.6 (confidence interval 1.2–2.2, \( P = 0.003 \)). ‘Forcing’ the second randomization into this model gives a hazard ratio for IFN maintenance vs no further treatment of 1.5 (95% confidence interval 0.7–2.9, \( P = 0.3 \)). The use of maintenance IFN did not therefore significantly influence survival. Considering all 4 treatment combinations in the Cox model, no combination was significantly better in terms of survival than standard treatment with CB followed by no further treatment (Table 8). Survival curves for the 4 patient groups are shown in Figure 4.

**Toxicity**

7 patients had to discontinue CB due to clinical toxicity. All subsequently developed recurrent lymphoma; 4 are well, 3 died of
progressive disease. Subjective Interferon toxicity with the initial treatment prevented continuation of the drug in 9 patients. 6 of the latter remain alive, 3/6 having been treated for recurrent lymphoma, 3 patients have died of progressive disease.

Haematological toxicity, resulting in an interruption in treatment or dose modification was significantly greater in patients receiving the combination (11/100: CB alone vs 37/104 for CB + IFN, $P < 0.001$). In addition, 5 patients experienced haematological toxicity with maintenance IFN necessitating interruption of treatment.

**DISCUSSION**

This study was undertaken to determine whether IFN, given initially in combination with, and then subsequent to, Chlorambucil, would alter the clinical course of patients with follicular lymphoma. Disappointingly, this objective was not achieved, no significant advantage being demonstrated for the addition of IFN to initial treatment or as maintenance therapy. An interim analysis had shown a significant difference in remission duration in favour of maintenance IFN (Price et al, 1991), however, with longer follow-up, this difference has been abrogated.

With regard to improving response rate, in this study, the addition of IFN not only did not help, but was associated with a lower response rate. The explanation for this may be the greater degree of haematological toxicity incurred with the combination, which in turn resulted in delays in administering Chlorambucil. Neither of the 2 other published studies in which IFN has been combined with an alkylating agent has in fact shown any advantage for the combination (Chisesi et al, 1991; Peterson et al, 1997). In contrast, the study reported by the ‘GELF’ Group (Solal-Celigny et al, 1993), did show a significantly higher response rate for IFN given with a more intensive, Adriamycin-containing regimen.

The rationale for adding IFN to alkylating agent therapy was based on 2 murine studies. Early work in AKR mice had demonstrated an ‘additive’ effect with a 200% increase in survival for mice treated with the combination of IFN and Cyclophosphamide (Gresser et al, 1978). A subsequent study (using the same combination of drugs) in a breast cancer xenograft growing in nude mice confirmed a synergistic response (Balkwill and Moodie, 1984). The latter study also indicated that the antitumor effect was greatest when the 2 drugs were used concurrently rather than sequentially.

The precise mechanisms of action of IFN in follicular lymphoma are unclear but probably represent a direct anti-proliferative effect (Balkwill and Taylor-Papidimiotriou, 1978; Balkwill et al, 1978, Taylor-Papidimiotriou, 1980). It is, however, possible that indirect effects on drug metabolism (Friedman et al, 1979; Singh and Renton, 1981; Marguet et al, 1983; Stolfi et al, 1983) are also involved.

Although it was not the case in the present study, as mentioned above, the use of IFN as part of initial treatment has been found to prolong remission duration (Smalley et al, 1992; Solal-Celigny et al, 1993; Anderson and Smalley, 1993; Solal-Celigny, 1997; Arranz et al, 1998) and in the ‘GELF’ study, survival (Solal-Celigny et al, 1993). However, the latter study also had a maintenance phase, it is therefore difficult to separate out the influence of continuing IFN from that of adding IFN to the initial therapy. With regard to prolongation of survival in the ‘GELF’ study, the question as to whether this reflects delay in time to transformation (to large B-cell histology), or a reduction in the incidence of transformation has been addressed; the rate of transformation was the same in the 2 treatment arms (Solal-Celigny, 1997).

Some studies were specifically designed to evaluate the use of maintenance IFN. Neither of the 2 other trials in which IFN maintenance followed treatment with an alkylating agent (Chlorambucil or Cyclophosphamide) show any advantage for maintenance IFN (Chisesi et al, 1991; Peterson et al, 1997). However, in a trial conducted by the European Organization for the Research and Treatment of Cancer, in which initial treatment comprised Cyclophosphamide, Vincristine and Prednisolone (CVP, with or without radiotherapy to large nodal masses), there was a trend towards improved time to progression in the IFN–treated group but this did not reach statistical significance (Hagenbeck et al, 1998). This was not the case in a study from Spain (Arranz et al, 1998), in which patients received CVP +/-IFN followed by a second randomization to IFN or to no further treatment. The German Low-grade Lymphoma Study Group trial (Unterhalt et al, 1996) does show a significant prolongation of disease-free survival with maintenance IFN (following initial therapy with either Prednimustine and Mitoxantrone, or CVP). However, this study is different from the rest; there being no fixed time limit for treatment with IFN, the drug being given until recurrence. In contrast, in the present study, there was in fact no difference in outcome between patients treated at the Christie Hospital where maintenance IFN was given only for 6 months and those treated at St Bartholomew’s Hospital where IFN was continued for 1 year (data not shown).

A Mexican study also shows both remission duration and survival to be significantly longer in a group of patients randomized to receive IFN after CR had been achieved with 3 sequential regimens followed in most patients by radiotherapy (Aviles et al, 1996). The obvious exception to these positive results is the trial conducted by the South-West Oncology Group (SWOG), in which the use of maintenance IFN given after the intensive, Adriamycin-containing regimen ‘PROMACE-MOPP’ (and in some patients, involved field radiotherapy) did not influence remission duration or survival (Fisher et al, 2000).

With regard to prognostic factors, the addition of Interferon did not confer benefit in any particular group. (It was not possible to assess the influence of a high LDH level, since LDH was not routinely measured at the time that this study began.) Older age was the only factor that correlated significantly with worse survival, in agreement with most previous analyses (Rudders et al, 1979; Gospodarowicz et al, 1984; Kantarjian et al, 1984; Gallagher et al, 1986; Lawrence et al, 1988; Steward et al, 1988; Lepage et al, 1990; Leonard et al, 1991; Romaguera et al, 1991; Soubeyran et al, 1991).

The discrepancies between the various studies may to some extent be explained by variations in study design and differences in selection criteria. Some trials included patients with low-grade lymphoma, but not necessarily only follicular lymphoma. In some, for example the ‘GELF’ study (Solal-Celigny et al, 1993), only patients considered to have an adverse prognosis were eligible, whereas in contrast, the ECOG study included patients with ‘indolent disease’ who were treated at the time of diagnosis, irrespective of whether there was a specific indication for treatment (Smalley et al, 1992).

In general however, the studies with the best results are those in which Interferon has been combined with, or followed, relatively intensive, initial chemotherapy (Smalley et al, 1992; Solal-Celigny...
et al, 1993; Aviles et al, 1996; Unterhalt et al, 1996), the SWOG study clearly being an exception (Fisher et al, 2000). The cumulative dose of IFN may also be important; the ‘SELF’ (Solal-Celigny et al, 1993), Mexican (Aviles et al, 1996) and German (Unterhalt et al, 1996) studies used a cumulative dose higher than that used in most of the others.

In order to clarify these discrepancies, a meta-analysis of 8 randomized trials has been conducted (Rohatiner et al, 1998). Only patients with follicular lymphoma were considered. No significant advantage was demonstrated for the addition of IFN to initial treatment. The use of IFN as part of initial therapy or as maintenance therapy did significantly improve remission duration ($P = 0.001$) and survival ($P = 0.002$) but there was significant heterogeneity between studies. This was clarified when it became apparent that the improvement was only true for studies in which a relatively intensive, Adriamycin (or equivalent) containing initial chemotherapy was used. With regard to ‘dose intensity’, in studies using $> 36 \times 10^8$ units of IFN per month, or a total cumulative dose $>1000 \times 10^8$ units, the addition of IFN significantly improved survival, but this effect ‘lost’ significance when the intensity of initial chemotherapy was included in a multivariate regression analysis (Gregory, 1999). Thus, the meta-analysis results confirm the impression that IFN is most effective when used with, or following, more intensive chemotherapy.

These results need to be seen within the context of other current experimental strategies for follicular lymphoma. High-dose treatment with autologous haemopoietic cell support (Rohatiner et al, 1994; Freedman et al, 1997, 1999; Apostolidis et al, 1999, 2000), Fludarabine-containing regimens that may induce ‘molecular remission’ (McLaughlin et al, 1996; Crawley et al, 2000; Grillo-Lopez et al, 2000), antibody therapy (McLaughlin et al, 1998; Rogers et al, 1996) and targeted irradiation (Press et al, 1995, Kaminski et al, 1996, Vose et al, 2000) are currently being evaluated. It is against this overall background that the place of Interferon must be considered.

ACKNOWLEDGEMENTS

We are most grateful to the medical and nursing staff involved in the clinical care of these patients and to the referring physicians, especially, Dr J Sweetenham, Professor Barry Hancock and Dr Elizabeth Miller. We thank Schering-Plough for their help in collation of data and Chris Sykes and Margaret Cresswell for preparing the manuscript.

REFERENCES

Andersen JW and Smalley RV (1993) Interferon Alfa plus chemotherapy for non-Hodgkin’s lymphoma five-year follow-up. N Engl J Med 329: 1821–1822
Apostolidis J, Foran JM, Johnson PWM, et al. (1999) Patterns of outcome following autologous bone marrow transplantation for follicular lymphoma. J Clin Oncol 17: 216
Apostolidis J, Gupta RK, Grenzellas D, et al. (2000) High-dose therapy with autologous bone marrow support as consolidation of remission in follicular lymphoma: long term clinical and molecular follow-up. J Clin Oncol 18: 527
Arranz R, Garcia-Alfonso P, Sobrino P, Zamora P, Carrion R, Garcia-Larana J, Perez G, Lopez J, Lavilla E, Lozano M, Rayon C, Colomer R, Baron MG, Flores E, Perez-Manga G and Fernandez-Ranada JM (1998) Role of Interferon Alfa-2b in the induction and maintenance treatment of low-grade non-Hodgkin’s lymphoma: Results from a prospective, multicenter trial with double randomization. J Clin Oncol 16: 1538–1546
Aviles A, Duque G, Talavera A and Guzman R (1996) Interferon Alfa 2b as maintenance therapy in low grade malignant lymphoma improves duration of remission and survival. Leuk Lymphoma 20: 495–499
Balkwill FR and Taylor-Papadimitriou J (1978) Interferon affects both G, and G, in cells stimulated from quiescence to growth. Nature (Lond) 274: 340
Balkwill FR and Moodie EM (1984) Positive interactions between human interferon and cyclophosphamid or adriamycin in a human tumor model system. Cancer Res 4: 904–908
Balkwill FR, Watling D and Taylor-Papadimitriou J (1978) Inhibition by lymphoblastoid Interferon of growth cells derived from human breast. Int J Cancer 258
Chiariglio MA and Pearson JW (1973) Cure of murine leukemia with drugs and interferon treatment. J Natl Cancer Inst 51: 1367–1368
Chiesi T, Capnisti G, Vespiagnani M and Cetto G (1987) Interferon alfa-2b and chlorambucil in the treatment of non-Hodgkin’s lymphoma. Invest New Drugs 5, Suppl: S35–40
Chiesi T, Congiu M, Contu A, Coser P, Moretti C, Porcellini A, Rancan L 6th, Salvagno L, Santini G and Vinante O (1991) 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. Non-Hodgkin’s Lymphoma Co-Operative Study Group. Eur J Cancer 27 Suppl 4, S31–3
Crawley CR, Foran JM, Gupta RK, et al. (2000) A phase II study to evaluate the combination of fludarabine, mitoxantrone and dexamethasone (FMD) in patients with follicular lymphoma. Ann Oncol 11: 1
Fisher RJ, Dana BW, LeBlanc M, Kjeldsberg C, Forman JD, Unger JM, Balcerzak ST, Gaynor ER, Roy V, and Miller T. Interferon alfa consolidation after intensive chemotherapy does not prolong the progression-free survival of patients with low-grade non-Hodgkin’s lymphoma: results of the Southwest Oncology Group randomized Phase III study 8809. J Clin Oncol 2000, 18(10): 2010
Foon KA, Sherwin SA, Abrams PA, Longo DL, Mer菲, Stevenson HC, Ochs JJ, Bottino GC, Schoenberger CS and Zeffren J, et al. (1984) Treatment of advanced non-Hodgkin’s lymphoma with recombinant leukocyte A interferon. N Engl J Med 311: 1148–1152
Freedman A, Gribben J, Neuberg D, Soiffer R, Anderson K, Fisher D, Schlossman R, Kroom M, Ritz J and Nadler L (1997) Long-term prolongation of disease-free and overall survival following autologous bone marrow transplantation in patients with advanced relapsed follicular lymphoma. Proc Am Soc Clin Oncol 16: 89a
Freedman AR, Neuberg D, Mauch P, et al. (1999) Long-term follow-up of autologous bone marrow transplantation in patients with relapsed follicular lymphoma. Blood 94: 3325
Friedman OM, Myles A and Colvin M (1979) Cyclophosphamide and raised phosphoramide mustards. In: F. Rosowsky (ed), Adv in Cancer Chem 143
Gallagher CJ, Gregory WM, Jones AE, Stansfeld AG, Richards MA, Dhalwil HS, Malpas JS and Lister TA (1986) Follicular lymphoma: Prognostic factors for response and survival. J Clin Oncol 4: 1470–1480
Gospodarowicz MK, Bush RS, Brown TC and Chua T (1984) Prognostic factors in nodular lymphomas: A multivariate analysis based on the Princess Margaret Hospital experience. Int J Radiat Oncol Biol Phys 10: 489–497
Gregory W (1999) Personal communication.
Gresser I, Brouty-Boye D, Thomas MT and Macieira-Coelho A (1970) Interferon and murine leukaemia VII. Gresser I, Brouty-Boye D, Thomas MT and Macierira-Coelho A (1970) Interferon and murine leukaemia VII. Nature 226: 97–99
Gutterman JU, Blumenschein GR and Alexanian R (1980) Leukocyte interferon-induced tumour regression in human metastatic breast cancer, multiple myeloma and malignant lymphoma. Ann Intern Med 93: 399–406
Hagenbeek A, Carde P, Somers R and Meerwaldt JH, et al. (1998) Maintenance of remission with human recombinant interferon alfa-2a in patients with stage III and IV low-grade malignant non-Hodgkin’s lymphoma. J Clin Oncol 16: 41 (abstract)
Horning SJ, Miergican TC and Krown SE (1985) Human interferon alpha in malignant lymphoma and Hodgkin’s disease. Cancer 56: 1305–1310
Hutkinisko MS, Zasadny KR, Francis IR, Fenner MC, Ross CW, Milik AW, Estes I, Tuck M, Regan D, Fisher S, Glenn SD and Wahl RL (1996) Iodine-131 - Anti-B1 radioimmunotherapy for B-cell lymphoma. J Clin Oncol 14: 1974–1981
Kantarjian HM, Mclaughlin P, Fuller LM, Dixon DO, Osborne BM and Cabanilllas FF (1984) Follicular large cell lymphoma: Analysis and prognostic factors in 62 patients. J Clin Oncol 2: 811–819

Kaplan E and Meier P (1958) Nonparametric estimation from incomplete observations. Am Stat Assoc J 53: 457–480

Lawrence TS, Urba WJ, Steinberg SM, Sundeen JT, Cossman J, Young RC and Glatstein E (1988) Retrospective analysis of stage I and II indolent lymphomas at the National Cancer Institute. Int J Radiat Oncol Biol Phys 14: 417–424

Leavitt RD, Ratanathathorn V, Ozer H, Ullmann JE, Portlock C, Myers JW, Kiesser D, Norred S, Spiegel RJ and Bonnem EM (1987) Alfa-2b Interferon in the treatment of Hodgkin’s disease and non-Hodgkin’s lymphoma. Semin Onc 14: 2 (suppl 2): 18–23

Leonard RC, Hayward RL, Prescott RJ and Wang J (1991) The identification of discrete prognostic groups in low grade non-Hodgkin’s lymphoma. Ann Oncol 2: 655–662

Lepage E, Sebban C, Gisselbrecht C, Couffier P, Harousseau JC, Byron PA and Boiron M (1990) Treatment of low grade non-Hodgkin’s lymphomas: assessment of Doxorubicin in a controlled trial. Hematol Oncol 8: 31–39

Lopez-Guillermo A, Cabanillas F, McLaughlin P et al. (2000) Molecular response to combination therapy is the most important factor predicting failure-free survival in indolent follicular lymphoma. Update of the MDACC series. Ann Oncol 11 (Supp 1): 137

Louie AC, Gallagher JG, Sikora K, Levy R, Rosenberg SA and Merigan TC (1981) Follow up observations on the effect of human leukocyte interferon in non-Hodgkin’s lymphoma. Blood 58: 712–718

Marguet RL, Schellekens H, Westbrook DL and Jeakel J (1983) Effect of treatment with Interferon and cyclophosphamide on the growth of a spontaneous liposarcoma in rats. Int J Cancer 31: 223

McLaughlin P, Hagemeister FB, Romaguera JE, et al. (1996) Fludarabine, cyclophosphamide versus cyclophosphamide plus interferon alfa-2b in a regimen containing doxorubicin in patients with advanced follicular lymphoma. New Eng J Med 329: 1608–1614

Mclarty P, Gohagan J, Schmitt M, Dolejs C and Vose JM, Wahl RL, Saleh M, et al. (2000) Multicentre Phase II study of Iodine 131 tositumomab for chemotherapy-relapsed/refractory low-grade and transformed follicular lymphoma. Blood 95: 1316–1318

O’Connell MJ, Colgan JP, Oken MM and Merigan TC (1986) Interferon – a2b (IFN-a2b) as initial therapy in combination with a regimen containing doxorubicin in patients with advanced follicular lymphoma. New Eng J Med 327: 1336–1341

Peterson BA, Petroni GR, Oken MM, Johnson JL, Barcos M and Cooper MR (1997) Recombinant interferon alfa-2b in the treatment of Hodgkin’s disease and non-Hodgkin’s lymphoma. Semin Oncol 24: 98–113

Peterson BA, Petroni GR, Oken MM, Johnson JL, Barcos M and Cooper MR (1997) Recombinant interferon alfa-2b in the treatment of Hodgkin’s disease and non-Hodgkin’s lymphoma. Semin Oncol 24: 98–113

Quesada JR, Hawkins M, Horning S, Alexanian R, Borden E, Merigan T, Adams F, Logan D, Wu Y, Tzankoff S, et al. (1991) Interferon – a2b (IFN-a2b) as initial therapy in combination with a regimen containing doxorubicin in patients with advanced follicular lymphoma. New Eng J Med 329: 1608–1614

Rajendran R, Marder R, Delellis RA, Gartner C, Goepfert H and Bonnem EM (1985) Nodular lymphoma and multiple myeloma. Clinical trial of recombinant leukocyte A interferon given as initial therapy. Annals of Oncology 1: 3–12

Rohatiner AZS, Johnson PWM, Price CGA, Arnott SJ, Amess JAL, Norton AJ, Dorey E, Adams K, Whelan JS, Matthews J, MacCallum PK, Oza AM and Lister TA (1994) Myeloidablative therapy with autologous bone marrow transplantation as consolidation therapy for recurrent follicular lymphoma. J Clin Oncol 12: 1177–1184

Solal-Celigny P (1997) Personal communication.

Peterson BA, Petroni GR, Oken MM, Johnson JL, Barcos M and Cooper MR (1997) Recombinant interferon alfa-2b in the treatment of Hodgkin’s disease and non-Hodgkin’s lymphoma. Semin Oncol 24: 98–113

Solvay P, Eghbali H, Bonichon F, Trojani M, Richard P and Hoerni B (1991) Low-grade follicular lymphomas: Analysis of prognosis in a series of 281 patients. Eur J Cancer 27: 1606–1613.

Spincolo JA, Cabanillas F, Dixon DO, Khorana SM, Mclaughlin P, Velasques WS, Hagemeister FB, Redman JR and Swan F Jr. (1992) Therapy of relapsed or refractory low-grade follicular lymphomas: Factors associated with complete remission, survival and time to treatment failure. Ann Oncol 3: 227–232

Stewart WP, Crowther D, McWilliam LJ, Jones JM, Deakin DP, Todd ID, Blackledge G, Wagstaff J, Scarfe JH and Harris M (1988) Maintenance chlorambucil after CVP in the management of advanced stage, low-grade histologic type non-Hodgkin’s lymphoma: A randomized prospective study with an assessment of prognostic factors. Cancer 64: 441–447

Stolfi RL, Martin DS, Sawyer RC and Spiegelman S (1983) Modulation of 5-fluorouracil-induced toxicity in mice with Interferon or with the Interferon inducer, polyinosinic-polyctydilic acid. Cancer Res 43: 561

Strander H, Adamsson U, Aparisi T, Brostrom LA, Cantell K, Einhorn S, Hall K, Ingimarsson S, Nilsone U and Sodergerg M (1979) Adjuvant interferon treatment of human osteosarcoma. Recent Result Cancer Res 68: 40–44

Taylor-Papdimitriou J (1980) Effects of interferons on cell cycle function and growth. In: I Gresser (ed). Interferon 2: 13–46

Unterhalt M, Hermann R, Koch P, Trumper L, Bodenstein H, DietzeFelfinger H, Landys K, Reub M, Vetter H, Maschmeyer G, Freund M, Neubauer A, Engert A, Stauder R, Herold M, Tiemann M, Parwaresch R, Stein H and Hiddemann W (1996) Long term interferon alpha maintenance prolongs remission duration in advanced low grade lymphomas and is related to the efficacy of initial cytoreductive chemotherapy. Blood 88 (Suppl 1): abstract 1801

Vose JM, Wahl RL, Saleh M, et al. (2000) Multicentre Phase II study of Iodine 131 tositumomab for chemotherapy-relapsed/refractory low-grade and transformed low-grade B-cell non-Hodgkin’s lymphomas. J Clin Oncol 18: 1316

Wagstaff J, Leynds P and Crowther D (1986) A phase II study of human recombinant DNA-a2 interferon in patients with low-grade non-Hodgkin’s lymphoma. Cancer Chemother Pharmacol 18: 54–58

© 2001 Cancer Research Campaign British Journal of Cancer (2001) 85(1), 29–35