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Natural Interferon Alfa as Maintenance Therapy for Small Cell Lung Cancer

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We performed a 3-armed phase III study between 1982 and 1990 to evaluate low dose natural interferon alfa (nIFN-α) as a maintenance therapy in small cell lung cancer (SCLC) following induction chemotherapy (CT) and consolidation radiotherapy (RT). All patients received four cycles of CT (cyclophosphamide, vincristine, etoposide), followed by split-course RT (55 Gy in 20 fractions over 7 weeks). 410 patients entered the study. 237 patients who completed induction CT + RT and were classified as responders (complete response + partial response) were randomly assigned to arm 1: low dose nIFN-α (91 patients); arm 2: maintenance CT, six cycles of CAP (cyclophosphamide, doxorubicin, cisplatin) (59 patients); or arm 3: control arm (no maintenance treatment) (87 patients). Halfway through the study the CAP arm was discontinued. There was no difference in median survival between the groups (IFN: 11 months, CAP: 11 months, control: 10 months), but a clear difference in long-term survival and in survival in the limited disease group, favouring nIFN-α maintenance therapy. Proportional hazards regression analysis also showed a significant effect of IFN treatment on survival. Our results suggest a role for nIFN-α in maintaining a clinically disease-free status achieved with other treatment modalities.
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INTRODUCTION

EFFECTIVE THERAPY for small cell lung cancer (SCLC) continues to be elusive and there has been little improvement in long-term survival during the past 5 years, despite the high initial response rates induced by chemotherapy [1]. Early recurrence remains frequent.

At present, neither the optimal duration of the primary therapy nor the utility of maintenance therapy are clear. The majority of clinical trials now maintain induction chemotherapy for periods varying from 4 to 6 months, instead of the 12 to 24 months used in the past, with the same therapeutic results [2, 3]. On the other hand, some randomised studies have shown that patients who received maintenance chemotherapy after induction therapy lived significantly longer than those who did not continue therapy [4, 5]. In studies where the same chemotherapy regime has been continued as maintenance therapy, the overall duration of survival of the patients has not changed [6, 7]. Moreover, in other randomised studies, maintenance therapy has caused a significant decrease in patient quality of life, without any improvement in duration of survival [8, 9]. A recently completed EORTC study confirmed the good results achieved with the CDE (cyclophosphamide, doxorubicin, etoposide) regime. In 445 patients randomly selected to receive 4 or 12 courses of CDE, the duration of remission was significantly longer for patients who received the 12 month course of therapy, although there was no difference in the rates of survival for the two groups [10].

There have been no indications that new chemotherapeutic agents improve duration of survival in SCLC. Interest has therefore focused on biological response modifiers [11, 12]. *In vitro* studies have shown that interferon augments the effects of chemotherapeutic agents in lung cancer cell lines [13]. Our previous results from clinical studies have suggested some biological activity for natural interferon alfa (nIFN-α) against SCLC when it was used as a single agent in a high dose induction treatment, followed by low dose maintenance therapy in previously untreated patients [14]. SCLC cells show a decrease or total absence of expression of class I histocompatibility antigens [15]. Interferon has been shown to induce these antigens both *in vitro* and *in vivo* [16]. This may be one mechanism by which interferon exerts an effect on the tumour in SCLC.

In some experimental tumour models, interferon inhibits metastatic dissemination rather than decreasing the mass of the primary tumour [17]. We, therefore, decided to investigate the possible role of maintenance therapy using interferon in increasing the survival of SCLC patients, by maintaining the clinical disease-free status achieved with other treatment modalities.

The report which follows brings up to date our earlier preliminary report on a 3-armed phase III study evaluating low dose nIFN-α used as maintenance therapy, following induction chemotherapy and consolidation radiotherapy, in patients with SCLC [18].

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PATIENTS AND METHODS

Criteria for eligibility

Patients, aged 75 years or less, having histologically or cytologically confirmed SCLC, were eligible for this study. Entry criteria included measurable or evaluable disease and a performance status of at least 60% on the Karnofsky scale. All clinical stages defined according to the TNM classification (1981) were accepted. Criteria for exclusion were: prior treatment with chemo- or radiotherapy; a previous or concomitant malignant tumour of different origin; or any serious concurrent disease.

Prior to entry, patients were required to have adequate renal and hepatic function and sufficient bone marrow reserve (leucocytes $\geq 3.5 \times 10^9$/l, platelets $\geq 100 \times 10^9$/l). Informed consent was obtained from all patients.

Treatment plan and randomisation

All patients, irrespective of clinical stage at entry, received three cycles of induction chemotherapy (CT) followed by split-course consolidation radiotherapy (RT). During the rest interval of the split-course regime, a fourth course of induction CT was administered. Patients showing complete response (CR) or partial response (PR) to the initial three cycles of chemotherapy, 2.5 months after entering the study, were randomly assigned at this point to one of the two regimes of maintenance therapy (nIFN-α, or another chemotherapy regimen); or to the control arm, where no maintenance treatment would be given. Randomisation was stratified according to extent of disease (limited/extensive). Assigned patients completed the induction therapy before starting the maintenance therapy programme. Patients who showed stable disease (SD) after three cycles of chemotherapy also continued induction therapy receiving the consolidation radiotherapy and a fourth cycle of chemotherapy. These patients were then re-evaluated for response on completion of radiotherapy, 5 months after entering the study. Those now showing CR or PR were randomly assigned to one of the two regimes of maintenance therapy or to the control group. Those patients continuing to be non-responders were not included in the study.

The induction chemotherapy consisted of cyclophosphamide 1200 mg/m^2 intravenously on day 1, vincristine 1.3 mg/m^2 intravenously on day 1 + day 8, etoposide 150 mg/m^2 intravenously on day 1, and 200 mg/m^2 orally on day 3. Cycles were given with a 4-week interval between each. The total radiation dose of the split-course regime was 55 Gy, given in 20 fractions over 7 weeks (10 × 3 Gy and 10 × 2.5 Gy with a 3 week break). The primary tumour, the mediastinum and the supraclavicular areas were included in the radiation volume. Two opposed fields were used. The spinal cord was shielded and individually shaped fields were used, to minimise radiation injury to normal tissue. Treatment was given by 8 MeV photons. Maintenance therapy, using nIFN-α [19], was given over 6 months, starting 2 weeks after completion of the induction treatment, at a dose of 3×10^6 U/day intramuscularly, 5 times a week for the first month and then at 6×10^6 U intramuscularly 3 times a week for 5 months.

The maintenance combination chemotherapy consisted of six cycles of CAP: cyclophosphamide 400 mg/m^2 intravenously, doxorubicin 40 mg/m^2 intravenously and cisplatin 40 mg/m^2 intravenously starting 2 weeks after completion of the induction therapy and repeated at monthly intervals.

Patients were considered evaluable for response if they had received a minimum of two cycles of induction chemotherapy. The evaluation of response followed WHO recommendations [20] and was carried out for all treatment groups according to a fixed time schedule: after two and three cycles of induction chemotherapy; on completion of radiotherapy; monthly during the 6 months following induction treatment; and every 3 months thereafter. Patients in the control arm were monitored and re-evaluated in the same way as those who received maintenance therapy. The duration of remission was calculated according to WHO guidelines [21]: CR, from the day CR was noted; PR, from the day induction therapy was begun. Survival time was measured from the day the patient was accepted into the study. Maintenance therapy with interferon or CAP was discontinued in patients showing progressive disease.

Patients who left the maintenance therapy study—for whatever reason—continued to be monitored, and were included in the statistics on relapse and survival.

Toxicity

Toxicities were graded according to WHO guidelines (1979 Geneva) and dose modifications were made according to the clinicians' recommendations.

Statistical methods

Actuarial survival was determined by the product limit method of Kaplan and Meier [22]. Comparison of survival curves was made by the Mantel–Haenszel (log-rank) test [23]. Intergroup differences were compared by the χ^2 test. Student's t-test was used to compare paired data. Proportional hazards regression analysis was used to test the simultaneous effect of several variables on survival [24]. P values > 0.05 were considered not statistically significant (NS).

RESULTS

From January 1982 to May 1990, 410 patients entered the study. 276 of these completed three cycles of induction chemotherapy. 215 were classified as responders and were randomly assigned to the maintenance therapy programme at this point. However, they had to complete the induction therapy programme (RT + 4th CT cycle) before they could start their assigned maintenance therapy. The patients with stable disease, who had achieved less than a partial response to the first three cycles of chemotherapy, also completed the induction therapy programme. Of this group, 22 patients responded during the rest of the induction treatment and were therefore also randomly assigned to the maintenance therapy programme. The total number of patients entered in the maintenance therapy programme was therefore 237 (215 + 22): 91 in the IFN arm; 59 in the CAP arm and 87 in the control arm (Table 1).

In May 1987, 3 years before entry into the study ended, the CAP arm was discontinued for two reasons. Firstly, to accelerate inclusion of patients in the IFN and control arms and secondly, patients in the CAP arm had shown no improvement in survival over those in the other arms, and their quality of life was considerably worse.

27/91 patients in the IFN arm, and 14/59 in the CAP arm did not start maintenance therapy, due to the fact that they had died, refused the treatment or because their disease had progressed or their condition deteriorated (Table 1). 6 patients in the control arm died or their disease progressed during this same time interval. 39 of the remaining 64 patients in the IFN arm discontinued treatment or died before completing the maintenance therapy course. Disease progression and/or death were the most frequent cause of discontinuation with 22/64 patients stopping treatment for this reason. 36/87 patients in the control

Table 1. Duration of maintenance therapy in 237 randomised patients

	IFN arm	CAP arm	O arm‡
No. of randomised patients	91	59	87
No. of patients failing to start assigned maintenance therapy	27	14	7
Reasons for failing to start			
Death *	19	10	6
Patient refusal	4	4	—
Fall in performance status	4	0	1
No. of patients leaving the study within 6 months of starting maintenance therapy†	39	29	37
Reasons for leaving			
Disease progression and/or death	22	20	36
Patient refusal	7	4	—
Fall in performance status	5	1	—
Side effects of therapy	4	3	—
Acute myocardial infarction	1	1	1
No. of patients completing 6 months in the maintenance therapy study	26	16	44
No. of patients alive 6 months after the start of the maintenance therapy study	53	36	44
Total	91	59	87

* Death between randomisation and the start of the maintenance therapy programme.

† Patients who left the maintenance therapy trial continued to be monitored and were included in the statistics on relapse and survival.

‡ Similar events during the same time period.

Table 2. Characteristics of 237 patients randomised to receive maintenance therapy

	IFN arm	CAP arm	O arm
n	91	59	87
Median age in years (range)	62 (42–75)	60 (43–74)	60 (46–75)
Sex (M/F)	72/19	47/12	64/23
Clinical stage			
LD (%)	56 (62)	33 (56)	56 (64)
ED	35	26	31
Performance status			
Karnofsky (%)			
90/100 (%)	29 (32)	21 (36)	36 (41)
80	31	20	25
<80	31	18	26
Tumour response to induction therapy			
CR (%)	41 (45)	30 (51)	39 (45)
PR	50	29	48
Relapse pattern *			
Local only (%)	9 (10)	8 (14)	5 (6)
Distant only	29	20	31
Both	15	14	25
Death without evident progression	38	17	26

LD = limited disease, ED = extensive disease.

* Site of the first relapse, occurring at any time after completion of induction therapy.

arm showed disease progression during the same period (Table 1).

26 of 53 patients who were alive 6 months after starting IFN maintenance therapy completed the full course of maintenance therapy with 48 patients completing at least 3 months of IFN maintenance therapy. In the control arm, 44 patients were observed for at least 6 months after completing induction treatment.

Patients' characteristics and tumour response to induction therapy are shown in Table 2. More patients achieved CR to the induction therapy in the CAP arm (51%) than in the IFN arm (45%) or the control arm (45%), but this difference was not significant. The patients with limited disease (LD) and very good performance status were evenly distributed between the arms of the study.

There were no significant differences in the relapse patterns between groups (Table 2).

Median survival for the patients in the IFN arm was 11 months, in the CAP arm 11 months and in the control arm 10 months (Fig. 1). The difference in actuarial survival was statistically marginally significant ($P = 0.048$). However, the hazard ratio for IFN/control was 0.702 with a 95% confidence interval from 0.500 to 0.981. Survival among patients with limited disease was significantly better in the IFN arm compared with the control arm (Fig. 2, $P = 0.021$). When survival was counted from the end of maintenance therapy the IFN arm also displayed a better survival than both other groups (Fig. 3). This difference in survival was statistically significant (logrank $P = 0.027$). There was a clear trend towards longer survival for patients in the IFN arm.

The crude 5 year survival rates were 11% for the IFN arm, 0% for the CAP arm and 2% for the control arm (95% confidence interval for the difference between IFN and control from 1 to 20%).

In the proportional hazards regression analysis, IFN treatment, extent of disease, T stage, node stage and performance status were the most important variables affecting survival (Table 3).

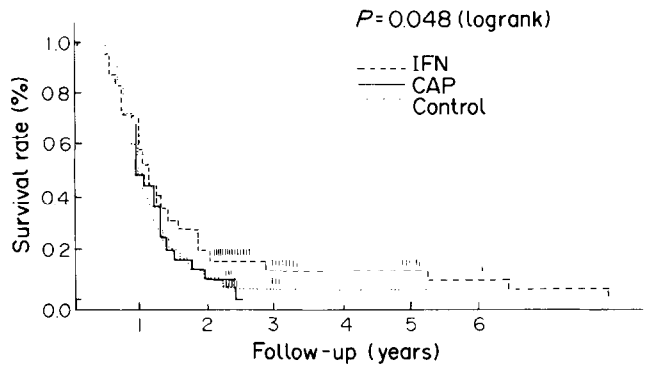

Fig. 1. Natural interferon alfa as maintenance therapy for SCLC: survival of responders to induction therapy (all randomised patients), calculated from the start of induction therapy ($n = 237$). ---- IFN maintenance therapy ($n = 91$); ____ CAP maintenance therapy ($n = 59$); ..... control ($n = 87$).

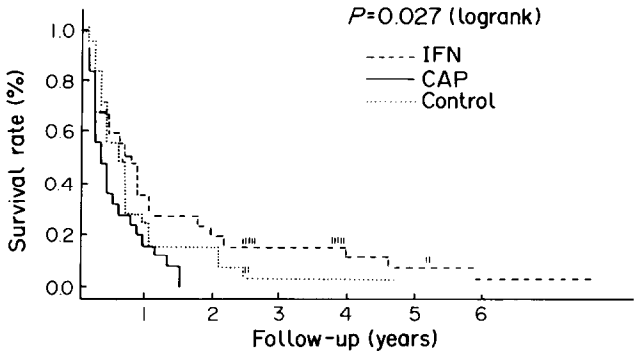

Fig. 2. Natural interferon alfa as maintenance therapy for SCLC: survival of patients who were alive at end of maintenance therapy, calculated from end of maintenance therapy (n = 74). ---- IFN maintenance therapy (n = 29); ____ CAP maintenance therapy (n = 24); ..... control (n = 21).

Neither haematological nor non-haematological toxicities were different from those reported in other studies.

Analysis of the causes of death after completion of induction therapy revealed that there were no IFN or CAP related deaths during maintenance treatment. 97% (57/59) of the deaths in the CAP arm, and 92% (72/78) of those in the IFN arm, were due to cancer. 2 patients died from acute myocardial infarction during maintenance therapy, but it could not be shown that the treatment was the cause. 99% (76/77) of deaths in the control arm were due to SCLC. 1 patient in this group, who lived for 5 years, died from another carcinoma after 62 months.

DISCUSSION

60–80% of patients suffering from SCLC can be expected to show an objective response to combination chemotherapy alone. About half of these will achieve complete remission, which is recognised to be one of the good prognostic factors in SCLC [25]. The objective response rate in our study was 52% after 3 cycles of chemotherapy, but only 12% of these were complete remissions. This low proportion of complete remissions may have been due (according to our present knowledge) to low dosage and less than optimal scheduling of etoposide [26].

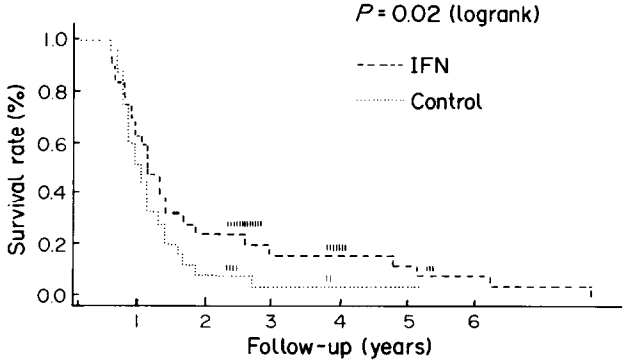

Fig. 3. Natural interferon alfa as maintenance therapy for SCLC: survival of patients with limited disease who responded to induction therapy, calculated from the start of induction therapy (n = 113). ---- IFN maintenance therapy (n = 56); ..... control (n = 57).

Table 3. Values of statistically significant regression coefficients from the proportional hazards of regression analysis of survival

Variable	Coefficient	S.E.
Interferon treatment	−0.4798	0.1743
Limited disease/extensive disease	−0.5110	0.1827
T3, T4/T1, T2	0.4874	0.1688
N2/N0	0.4692	0.2246
Karnofsky %	−0.0149	0.0069

Thoracic radiotherapy was combined with chemotherapy for all patients. This was valuable in that it increased the local response rate. However, in many cases the 11–12 week interruption in systemic treatment may have allowed metastases to develop at other sites, even when CR had been achieved at the primary site.

There is no clear consensus in the literature as to how long initial chemotherapy should continue for patients who achieve remission [2, 3, 7, 8, 27, 28]. There have been trials in which the drugs inducing remission, and therefore active against SCLC, continued to be administered as maintenance therapy [7]. On the other hand, maintenance chemotherapy has been administered using drugs other than those used during the induction therapy [5]. In our study, we substituted a biological response modifier, nIFN-α, for the usual maintenance chemotherapy. CAP was chosen for comparison because at the beginning of 1980 it was thought to be one of the most effective combinations against lung cancer. It could also be given in lower doses on an out-patient basis. The IFN dose was selected according to our previous experience of its efficacy against SCLC tumours and of patient tolerance [14, 18], and the good results obtained in other studies involving prolonged low dose IFN-α treatment for hairy cell leukemia [29]. Our pilot studies suggested that the dose chosen was safe and relatively tolerable for the patients.

The results show that there was a clear trend towards longer survival for patients who continued IFN maintenance therapy for the full 6 months, compared with those who received CAP maintenance therapy or no maintenance therapy at all.

There was only a marginally significant increase in actuarial survival for the IFN group as a whole. In the limited disease group the difference in survival was clear and significant. There was also an increase in absolute long term survival. Interferon therefore appears to benefit those patients with a good prognosis.

Haematological toxicity was more of a problem during induction therapy than during maintenance therapy. No patient discontinued maintenance therapy because of haematological toxicity, but there were 9 (2%) deaths due to myelosuppression during induction therapy. Some patients refused maintenance therapy because of peripheral polyneuropathy caused by vincristine given during the induction period.

In retrospect, we believe that the interferon therapy was started much too late—about 6 months after the patients had entered the study. This long delay, early randomisation and the decision not to give maintenance treatment to patients with progressive disease all meant that many patients assigned to the interferon arm in fact received no or only a few IFN injections. In those patients interferon obviously had no chance to show its potentially beneficial effects. The interferon therapy was much

too short. This was in part due to the shortage of interferon in 1981, when the present trial was designed. Even in malignancies such as hairy cell leukemia, which are highly responsive to interferon, a very long period of treatment is required. It was also our impression that relapse or recurrence began within a few months of cessation of interferon treatment in many of our SCLC patients.

It is encouraging that the interferon therapy prolonged the life of a proportion of the patients. To exploit the therapeutic potential of interferon in SCLC more effectively, we embarked on a new study in May 1990 in which interferon is a part of the induction therapy and interferon treatment is continued until the patients die.

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