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Interferons Combined with Chemotherapy in the Treatment of Stage III–IV Non-small Cell Lung Cancer—a Randomised Study

Maija Halme, Paula K. Maasilta, Seppo O. Pyrhönen and Karin V. Mattson

80 patients with previously untreated stage III–IV non-small cell lung cancer (NSCLC) were randomly assigned to receive chemotherapy (CT) alone (arm I: 26 patients) or the same CT combined with either interferon (IFN)-γ (arm II: 27 patients) or with both IFN-γ and IFN-α (arm III: 27 patients). The CT comprised cisplatin 60 mg/m² intravenously (i.v.) day 1 and etoposide 100 mg/m² i.v. days 1, 3 and 5, once every 28 days; the IFN therapy comprised either recombinant IFN-γ1b 0.2 mg/m², subcutaneously, three times a week until day 25, or recombinant IFN-α2c 6 × 10⁶ U given according to the same schedule, and simultaneously with IFN-γ. A maximum of six cycles were given. The treatment was discontinued if progressive disease (PD) was demonstrated. The mean numbers of cycles per patient given in the different arms were 3.6 (arm I), 3.0 (arm II) and 2.9 (arm III). The main reason for discontinuation in all arms was PD. 17 (28%) of the 61 evaluable patients achieved partial responses (35% in arm I, 29% in arm II and 35% in arm III, non-significant). No complete response was recorded. Haematological toxicity was dose-limiting in all arms: leucopenia (WHO grade 3) was observed universally, but more frequently in arm III (in 18% of cycles given). Only two episodes of grade 4 leucopenia were seen (arms II and III) and six episodes of grade 3–4 thrombocytopenia (arm III). Median survival was 6–7 months in all arms. The survival curve for arm II was slightly more favourable (non-significant) than those for other arms. The addition of IFN-γ alone or IFN-α plus IFN-γ to platinum-based CT did not improve response rates nor did it produce any significant survival benefit for patients with NSCLC. Increased haematological toxicity was observed when both IFNs were administered concomitantly with CT.

Key words: cisplatin, etoposide, interferon-α, interferon-γ, NSCLC
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INTRODUCTION

THE REASON for our inability to cure more than 10–15% of all lung cancer patients is the presence of distant metastases at the time of diagnosis. Thus, systemic therapy must be the basis of any successful programme to cure more lung cancer patients, and to improve the survival of those patients who cannot be cured.

Correspondence to M. Halme.
M. Halme, P.K. Maasilta and K.V. Mattson are at the Department of Pulmonary Medicine; and S.O. Pyrhönen is at the Department of Radiotherapy and Oncology, Helsinki University Central Hospital, Haartmaninkatu 4, SF-00290, Helsinki, Finland.
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Most drug combinations evaluated in the 1970s comprised inactive agents. These combinations were never shown to prolong the survival of patients with non-small cell lung cancer (NSCLC) at any stage in its course, whether used alone or in combination with surgery or radiotherapy [1].

Recent studies have shown that cisplatin-based chemotherapy improves survival for patients at all stages of NSCLC. For patients with advanced disease, cisplatin-based combinations have improved survival compared with best supportive care [2].

Chemotherapy is most active in patients who have received no prior chemotherapy and who have other well-documented positive prognostic factors. The response rate is not dependent upon the histological variety of NSCLC [3]. New treatment approaches are certainly needed to improve the outcome for the

majority of patients. Various biological response modifiers, interferons (IFN) amongst others, are being evaluated as new treatment modalities.

IFNs can exert a wide range of regulatory actions on normal, cancer and host immune defence cells, resulting in inhibition of cell growth, alterations in cell structure, cell differentiation and metabolism, enhancement of cell antigen expression and modulation of immunological response [4].

IFN-γ interacts with a distinct membrane receptor, and differs from IFN-α and IFN-β with respect to its antiproliferative and immunomodulatory properties [5].

In a phase II study using high-dose IFN-γ as a single agent against NSCLC, Mattson *et al.* [6] reported one partial response in 10 patients after 12 weeks of treatment. This is in contrast to the negative results obtained in several studies using IFN-α as a single agent against NSCLC [7, 8].

Synergistic or additive interactions between IFN-α and other cytokines or cytotoxic drugs, particularly cisplatin, have been demonstrated in *in vitro* studies [9–11] and in laboratory animals [12, 13]. Although data on optimal scheduling of these two classes of anti-tumour agent and the mechanisms of interaction are not available from experimental systems, clinical trials have been performed [14–16] which indicate that it is possible to give alpha IFNs in combination with cisplatin. The combination of IFN-α and -γ without chemotherapy has been studied in the treatment of metastatic melanoma [17]. In contrast to the synergistic effect seen *in vitro*, no *in vivo* anti-tumour effect has been documented. To further test this hypothesis of synergism between cytokines and cytostatic drugs clinically, we performed a randomised phase II study of IFN-α, IFN-γ and cisplatin-based chemotherapy for NSCLC.

MATERIALS AND METHODS

Patients

All patients had inoperable, previously untreated, histologically or cytologically confirmed NSCLC. The tumour was assessed using the international staging system [18] and confirmed by bronchoscopy and computed tomography. All tumours had to be measurable bi- or unidimensionally. Additional entry criteria were age ≤ 70 years, Karnofsky index ≥ 60%, no major cardiovascular disease and expected survival ≥ 2 months. The presence of brain metastases was not an exclusion criterion. A white blood count (WBC) ≥ 4.0×10^9/l, platelet count ≥ 100×10^9/l, creatinine serum level ≤ 115 μmol/l and creatinine clearance ≥ 1.4/ml/s/1.73 m^2 were laboratory requirements.

Study design

Patients were randomly assigned to one of the following treatment arms: I: chemotherapy alone, II: chemotherapy and IFN-γ, III chemotherapy and IFN-α plus IFN-γ. No stratifications were performed. All patients gave their written consent, and the study was approved by the ethical committees of both the participating departments.

Therapy

Chemotherapy. Cisplatin (60 mg/m^2) was administered intravenously on day 1 of each cycle together with etoposide (100 mg/m^2) on days 1, 3 and 5 of the 28-day cycle. The protocol allowed a maximum of six cycles. Treatment response was evaluated after every two cycles. If a partial or complete response had not been achieved after four cycles, treatment was stopped. Treatment was discontinued at any time if progressive disease was documented. If there was not full haematological recovery by day 1 of the next cycle, chemotherapy was postponed by 1 week. The treatment could not be postponed by more than 2 weeks. Individual dose modifications in chemotherapy, based on the nadir values of WBC and/or platelets between cycles, were also allowed.

IFN-γ. Recombinant IFN-γ1b (Boehringer Ingelheim, Ingelheim am Rhein, Germany) with specific activity 20×10^6 U/mg protein was given at a dose of 0.2 mg/m^2 subcutaneously (s.c.) three times a week (day 1, 3, 5, 8, 10, 12 etc), simultaneously with chemotherapy. IFN-γ treatment was continued until day 25 of the last chemotherapy cycle.

IFN-α. Recombinant IFN-α 2c (Boehringer Ingelheim) with specific activity of 333×10^6 U/mg protein was given at a dose of 6×10^6 U s.c. three times a week (day 1, 3, 5, 8, 10, 12 etc), simultaneously with chemotherapy and IFN-γ therapy. IFN-α treatment was also continued until day 25 of the last chemotherapy cycle.

Modern anti-emetics were given routinely with the chemotherapy. Paracetamol was also given routinely, to control or prevent IFN-induced flu-like reactions.

Statistical methods

The estimates of life expectancy were calculated by the Kaplan–Meier product limit method using the BMDP statistical software (program 1L) [19]. Estimates for prognostic factors (age, sex, Karnofsky index, tumour histology, clinical stage, therapy) were calculated using Cox's proportional hazards model (BMDP program 2L).

RESULTS

A total of 80 patients were entered in the trial. The clinical characteristics of the 80 patients show that the three groups were fairly well balanced with respect to age, sex, disease status and performance status (Table 1). There were fewer female patients,

Table 1. Clinical characteristics of 80 patients with non-small cell lung cancer randomly assigned to receive chemotherapy alone (I), *or chemotherapy combined with either* IFN-γ (II) *or* IFN-α *and* IFN-γ (III)

	Total	I	II	III
n	80	26	27	27
Sex				
Male	58	17 (29%)	19 (33%)	22 (38%)
Female	22	9 (41%)	8 (36%)	5 (23%)
Age (years)				
Mean		55	56	58
Range		40–69	37–69	42–70
Histology				
Adeno	41 (51%)	14 (34%)	16 (39%)	11 (27%)
Squamous	31 (39%)	9 (29%)	9 (29%)	13 (42%)
Large	8 (10%)	3 (38%)	2 (25%)	3 (38%)
Clinical stage				
IIIa	1 (1%)	—	1	—
IIIb	14 (18%)	3	5	6
IV	65 (81%)	23	21	21
Karnofsky index				
100–90%	34 (43%)	12 (35%)	14 (41%)	8 (24%)
80–60%	46 (58%)	14 (30%)	13 (28%)	19 (41%)

more squamous cell tumours and more patients with a low performance score in arm III. 11 patients never started treatment. The reasons for not starting treatment were either patient refusal or protocol violation, i.e. the patient did not meet the entry criteria (arm I: 2 patients, arm II: 2 patients, and arm III: 7 patients). For details, see tumour response.

The total number of chemotherapy cycles administered was 92 in arm I, 77 in arm II and 77 in arm III. The maximum six cycles were given to 23/68 patients (arm I: 9, arm II: 7, arm III: 7). The average numbers of cycles given in the different arms were 3.6 in arm I, 3.0 in arm II and 2.9 in arm III. The mean percentages of the total planned dose of the cisplatin-etoposide chemotherapy given were 90–88% for arm I, 91–87% for arm II and 84–81% for arm III. The patients received 73% of the planned IFN-γ in arm II, and 70% of the planned IFN-α and 69% of the planned IFN-γ in arm III.

The invariable reason for stopping treatment was progressive disease (PD). 1 patient in arm II was excluded from further treatment because she took too long to recover from grade 3 leucopenia, and 1 patient in arm III was withdrawn because of grade 4 renal toxicity, which was reversible. 1 patient in each of arms II and III stopped IFN treatment because of the side-effects, i.e. fever. They continued the chemotherapy until progression was confirmed.

32 patients received other oncological treatment after terminating the protocol treatment. Different non-platinum-based chemotherapy was given to 13 patients: arm I (chemotherapy alone): 7 patients; arm II (chemotherapy + IFN-γ): 2 patients; arm III (chemotherapy + IFN-α + IFN-γ): 4 patients. Figures for palliative radiotherapy were: arm I: 5 patients, arm II: 5 patients, arm III: 7 patients. 2 patients in each of arms I and II and 1 patient in arm III received both radiotherapy and another chemotherapy regimen.

Tumour response

61 patients were evaluable for response. No complete response was achieved. Partial responses were as follows: 6/22 in arm I; 5/21 in arm II; 6/18 in arm III (Table 2). There were six partial responses in patients with squamous cell carcinoma (2 patients in each arm), 10 in patients with adenocarcinoma (arm I: 3, arm II: 3, arm III: 4 patients) and one in patients with large cell carcinoma (arm I). Differences in response rate between the treatment arms or for the different histologies were non-significant. The maximum response was usually observed after two cycles with no difference between the arms. The median duration of response for the patients achieving partial responses was 27 weeks in arm I, 36 weeks in arm II and 28 weeks in arm III, as calculated from the first treatment day to the documentation of PD. Median time to progression was 16 weeks for all evaluable patients (arm I: 17, arm II: 12, arm III: 17).

The remaining 19 patients could not be evaluated for response; 8 because of early death (arm I: 2, arm II: 4, arm III: 2 patients), 5 because they refused treatment at the beginning of the first cycle (arm I: 0, arm II: 1, arm III: 5 patients) and 6 because of protocol violation (arm I: 2, arm II: 1, arm III: 2 patients).

Toxicity

69 patients were evaluable for toxicity. Leucopenia (grade 3) occurred in 14 out of 77 cycles (18%) in patients receiving chemotherapy with both IFNs (arm III) as opposed to 3 out of 77 (4%) in arm II (chemotherapy and IFN-γ alone) and 5 out of 92 (5%) in arm I (chemotherapy alone). Grade 4 leucopenia was seen once in each of arms II and III. The same trend was seen in the platelet values: grade 3–4 thrombocytopenia was only seen in arm III (Table 2).

Table 2. Number of chemotherapy cycles, chemotherapy and IFN doses, response rates and toxicity grades (WHO criteria) in patients with NSCLC randomly assigned to receive chemotherapy alone (I) *or chemotherapy combined with either* IFN-γ (II) *or* IFN-α *and* IFN-γ (III)

	Total	I	II	III
Chemotherapy cycles administered				
All	246	92	77	77
Mean/patient	3.2	3.6	3.0	2.9
Patients given six cycles	23	9	7	7
Chemotherapy dose (mean % of planned)				
Cisplatin		90	91	84
Etoposide		88	87	81
Interferon dose (mean % of planned)				
IFN-α				70
IFN-γ			73	69
Evaluable for response				
Total	61	22	21	18
Partial response	17 (28%)	6	5	6
Stable disease	25 (41%)	10	6	9
Progressive disease	19 (31%)	6	10	3
Non-evaluable for response				
Total	19	4	6	9
Refusal/protocol violation	11	2	2	7
Early death	8	2	4	2
Median duration of response (weeks)	28	27	36	28
Median time to progression (weeks)	16	17	12	17
Median survival (months)	6.5	7	6	7
Evaluable for toxicity				
Total	69	24	25	20
Leucopenia				
Grade 3		5	3	14
Grade 4		—	1	1
Thrombocytopenia				
Grade 3		—	—	2
Grade 4		—	—	4
Nausea and vomiting				
Grade 3		11	13	7

There were no major differences in the incidence of nausea and vomiting in the different arms of the study, although the incidence of grade 3 nausea was slightly higher in arm II (arm I: 12%, arm II: 17%, arm III: 9%). Fever (grade 3) and renal toxicity (grade 4) were each only seen in 1 patient, in arms II and III, respectively.

Survival

Median survival was 7 months in arm I, 6 months in arm II and 7 months in arm III (Table 2). The differences (in survival) between the arms were statistically non-significant. Figure 1 shows the actuarial survival curves for the three arms of the study. A trend towards longer survival in arm II can be seen, but the difference is not statistically significant. According to Cox's proportional hazards model only age > 45 years ($P = 0.0034$) and Karnofsky index $> 80\%$ ($P = 0.0473$) had significant prognostic influence.

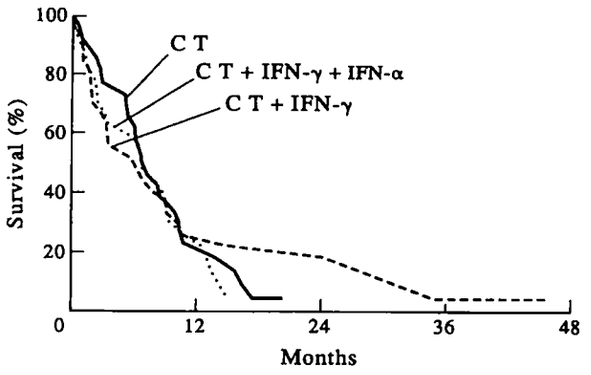

Fig. 1. Kaplan–Meier survival curves of 80 patients with NSCLC randomly assigned to receive chemotherapy alone or chemotherapy combined with either IFN-γ or IFN-γ and IFN-α.

DISCUSSION

At the present time there is no standard treatment for stage III–IV NSCLC. Recent studies have shown that cisplatin-based chemotherapy improves survival for patients at all stages of NSCLC [3]. Carmichael *et al.* demonstrated potentiation of cisplatin treatment by IFN-α in human NSCLC xenografts [12], and Bowman *et al.* showed the same in advanced NSCLC [15]. Some positive experiences of IFN-γ as a single agent or IFN-α combined with other conventional therapies against NSCLC have been reported [6, 20]. The promising results from clinical studies of combining IFNs with chemotherapy in other solid tumours [21–23], and interesting studies of potentiation achieved using combination cytokine treatment both *in vivo* and *in vitro* [24, 25], prompted us to perform this study of chemotherapy alone or combined with either one or two cytokines. The study was designed as a randomised phase II trial with cisplatin-based chemotherapy as the control arm, and the same chemotherapy with either IFN-γ alone or with IFN-α and IFN-γ as the other two arms.

All three arms were moderately well balanced with respect to the drop-out of patients due to early death, protocol violation or late refusal after random assignment. Only 34% of patients who started the treatment prescribed by the protocol received the full six cycles. Progressive disease caused treatment to be discontinued in more cases than toxicity. 61 out of 80 randomly assigned patients were evaluable for response. No significant augmentation of response could be demonstrated by combining IFN-α and IFN-γ or IFN-γ alone with chemotherapy, when compared with the response to chemotherapy alone. Our data are also in contrast with the results of a non-random study of cisplatin and IFN-α for 68 patients with NSCLC, reported by Bowman *et al.* [15]. They demonstrated a response rate of 46%, noticeably in patients having squamous cell carcinoma. We did not see any differences in response favouring a particular histology. One possible explanation for the better result in Bowman's study may be the higher dose of cisplatin they used (100 mg/m^2). This does not, however, explain the more favourable result for squamous cell carcinoma.

Haematological toxicity is a well-known side-effect of both chemotherapy and IFN therapy. In our study, it was moderate but clearly greater in arm III (patients receiving both IFNs), indicating a potentiation of haematological toxicity when two IFNs are administered with chemotherapy. Ernstoff *et al.* [24] showed dose-limiting toxicity including leucopenia etc. in patients with metastatic renal cell carcinoma receiving high doses of IFNs [IFN-α ≤ 20 × 10^6 U, s.c., three times a week and IFN-γ ≤ 1 mg/m^2 intravenously (i.v.) for 5 days every third week] without chemotherapy. Their findings also suggested that reduced toxicity is encountered when these agents are administered sequentially rather than simultaneously [24]. This is in accordance with our results. In addition, Schiller *et al.* have shown that pretreatment with a combination of IFN-β and IFN-γ before two cycles of cisplatin and etoposide produces more haematological toxicity during chemotherapy [26].

Our patients tolerated the IFN treatment fairly well, and only 2 out of the 54 patients receiving IFN wanted to stop the treatment because of the side-effects, i.e. fever. The one episode of renal toxicity seen in our study was interpreted as a side-effect of cisplatin.

Only 69–73% of the planned total dose of IFN was administered because a number of doses were omitted during chemotherapy-induced leucopenia. The dose of IFN-γ in our study (0.2 mg/m^2 s.c. three times a week) was chosen by using the data from our pilot study which demonstrated that cardiotoxicity is caused by high doses of IFN-γ [6]. We considered this to be a low dose, but it was still higher than that recently recommended for achieving the best cytotoxic effect by Maluish *et al.* [27]. In their study of melanoma patients, IFN-γ was shown to be more effective at a dose of 0.1 mg/m^2 s.c. than at 0.25 mg/m^2 by measuring such parameters as natural killer cell activity, hydrogen peroxide production by monocytes, and changes in expression of Fc receptors and human leucocyte class II antigen on monocytes. On the other hand, the clear response achieved in our study using a single high dose of IFN-γ for NSCLC patients [6] would suggest a preference for higher doses. The dose of IFN-α (18 μg s.c. = 6 × 10^6 U) used in our study was also high compared with the dose used by Bowman *et al.* for example, who showed a potentiation of cisplatin activity by IFN-α [15]. In a dose escalation study of subcutaneously administered recombinant IFN-α in patients with metastatic carcinoid tumour, Veenhof *et al.* demonstrated that a dose of 3 × 10^6 U three times a week was the most effective [28]. If we consider these results, our choice of IFN dose was probably not optimal.

The patients in our study were allowed to receive other treatments after the termination of the trial. The main indication for these treatments was palliation (radiotherapy), but some patients also received another chemotherapy regime because they had good performance status and were willing. In retrospect, the arms remained moderately well balanced even after other treatments, and we do not expect these treatments to introduce any major bias in the interpretation of the survival rates. There was a trend, although not significant, towards longer survival for patients receiving chemotherapy and IFN-γ in our study. If one could expect any improvement in survival rate based on the treatments given after the trial termination, it would be for arm I patients receiving more non-protocol chemotherapy.

The response rates in the different arms (PRs for arms I, II and III, 6/22, 5/21, 6/18, respectively) does not suggest a trend toward longer survival in arm II. Pyrhönen *et al.* [29] have reported a similar result: a fairly long median survival for patients receiving natural IFN-α for metastatic melanoma, despite a very low (3%) response rate. A regression of lung metastases from melanoma was also demonstrated after cessation of IFN treatment [29]. In small cell lung cancer, maintainance therapy with natural IFN-α after induction chemotherapy and consolidation radiotherapy has also been shown to prolong survival [30]. No late responses were seen in our study in

which IFN treatment was discontinued at the same time as chemotherapy. The maximum responses usually appeared after two to three cycles.

In conclusion, combining either IFN-γ (0.2 mg/m^2 three times a week) or both IFN-γ and IFN-α (6×10^6 U three times a week) given s.c. with cisplatin and etoposide did not improve response rates in stage III–IV NSCLC. Instead, the combination of chemotherapy with both IFNs was shown to increase haematological toxicity compared to chemotherapy alone or to chemotherapy with IFN-γ. A trend towards longer survival was seen for patients receiving chemotherapy and IFN-γ, but no statistically significant difference favouring this arm could be demonstrated. Further investigations, especially in optimal dosing and treatment length, are still needed to confirm the role of IFNs with chemotherapy for NSCLC.

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