Adjunctive interferon-α-2c in stage IIIB/IV small-cell lung cancer: a phase III trial

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ABSTRACT: Preliminary studies have shown bioactivity of interferons (IFNs) in the treatment of small-cell lung cancer (SCLC). The aim of the present study was to determine whether, in patients with advanced SCLC, a combination of recombinant IFN-α-2c and standard induction chemotherapy would improve response rates and survival at acceptable toxicity.

Of the 85 patients recruited by 11 centres in Austria, 77 were evaluable for response after induction therapy; of these, 43 were randomized to receive the combined treatment (three cycles each of cyclophosphamide/vincristine/doxorubicin and cisplatin/etoposide plus subcutaneous IFN-α-2c), and 34 received chemotherapy alone.

After the induction phase, patients in the IFN arm had higher rates of complete (30 vs 15%) and partial remission (42 vs 29%) than those who received chemotherapy alone. Accordingly, there was a lower rate of progressive disease in the interferon arm (21 vs 44%; p<0.05). Whilst there were no significant differences in time to progression (7.6 vs 5.4 months) patients in the IFN arm survived longer than those in the chemotherapy arm (p<0.02). Six of the patients treated with IFN (14%) survived for more than 2 yrs, whereas none in the chemotherapy arm did.

We conclude that the addition of interferon-α-2c to induction chemotherapy may improve response rates and survival in advanced small-cell lung cancer.


The overall effect of therapy on survival in small-cell lung cancer (SCLC) has remained unsatisfactory despite the continued introduction of new chemotherapy protocols, the use of haematopoetic growth factors and even bone marrow transplantation [1–3]. Whilst most patients respond to chemotherapy initially, most experience relapses, which are neither treatable nor preventable with conventional chemotherapy [4]. Therefore, new principles are being sought in the treatment of this disease.

Biological response modifiers, notably interferons (IFNs), have been tested extensively in cancer treatment [5, 6]. IFNs exert a wide range of regulatory actions on normal, cancer, and host immune defence cells, resulting in inhibition of cell growth as well as alteration of cell structure, surface antigen expression, differentiation and function [7, 8]. Antitumour activity of IFNs has been shown in human SCLC cell lines [9, 10], and early clinical studies have suggested that IFN-α as a single agent can delay lung cancer growth [11, 12]. Synergistic or additive interactions between IFN-α and cytotoxic drugs, particularly cisplatin, have been demonstrated in the experimental setting [13–18], and in clinical phase II studies [19]. However, only few randomized clinical trials have been conducted to evaluate the possible advantage of adding IFN-α to conventional induction therapy [20].

The aim of the present study was to determine whether, in patients with advanced SCLC, a combination of recombinant IFN-α-2c and standard induction chemotherapy would improve response rates and survival at acceptable toxicity.

Patients and methods

Study subjects

Previously untreated patients with histology confirmed SCLC, World Health Organization (WHO) stages IIIB and IV, were eligible. Exclusion criteria included: age >70 yrs, symptomatic central nervous system (CNS) metastasis; Karnofsky index <70; creatinine clearance <60 mL·min⁻¹; and serious concomitant disease. Eighty five patients were recruited by 11 centres in Austria. No data sheets were received from seven subjects, and one was removed from the study during the first chemotherapy cycle due to acute myocardial infarction. The remaining 77 patients were evaluable for assessment of response and toxicity. Patients' characteristics are summarized in table 1.

Pretreatment investigations included: general medical examination; chest radiography; computed tomography;
(CT) of the chest, upper abdomen and CNS; tissue sampling by bronchoscopy or mediastinoscopy; and a bone scan. Histological slides and radiography/CT films were interpreted by local specialists at the participating centres, who were not involved in the treatment of the patients.

**Study design**

A randomized, nonblinded trial was conducted. Randomization was performed centrally at the Institute of Biostatistics, University of Innsbruck. Randomization was stratified for stage (IIIb vs IV) and the presence or absence of liver and/or CNS metastasis.

**Methods**

**Induction therapy.** All patients received induction chemotherapy similar to the regimen used by EVANS et al. [21]. In both arms, intravenous chemotherapy comprised cyclophosphamide (1,000 mg·m⁻²), doxorubicin (Adriamycin) (50 mg·m⁻²) and vincristine (2 mg) ("CAV") given on Day 1; alternating with etoposide (E) (100 mg·m⁻²) and cisplatin (P) (25 mg·m⁻²) ("EP") given on Days 22, 24 and 26. This combination was repeated twice at three weekly intervals. Patients in the "interferon arm" received additional IFN-α-2c (Berofor; Bender, Vienna, Austria; specific activity 0.23 M IU·µg⁻¹ protein), 15 µg thrice weekly, for 6 months or until disease progression was noted, the patients were re-evaluated by CT scans of brain, thorax, and upper abdomen. Antiemetic treatment was not standardized. Paracetamol, 500 mg as needed, was given to treat IFN-related flu-like symptoms. Chemotherapy was postponed in case of incomplete haematological recovery (leucocyte count <3,000 cells·µl⁻¹, platelet count <100,000 platelets·µl⁻¹). After completion of the induction phase or whenever disease progression was noted, the patients were re-evaluated by CT scans of brain, thorax, and upper abdomen.

**Maintenance phase.** Patients in the IFN arm who achieved complete or partial response after induction therapy received local radiotherapy to the tumour and regional lymph nodes (50.4 Gy in daily fractions of 1.8 Gy, given 5 days-week⁻¹).

**Radiotherapy.** Patients with stage IIIB disease showing complete or partial response after induction therapy received local radiotherapy to the tumour and regional lymph nodes (50.4 Gy in daily fractions of 1.8 Gy, given 5 days-week⁻¹).

**Time frame and end points.** The study was initiated in March 1990. It was intended that 125 patients would be investigated in each treatment arm. This would have made it possible to find an improvement in median survival from 9 to 13 months at a significance level of 0.05 and a statistical power of 80%. A comparison between the actual number of randomized patients (from October 1992) with the expected number of patients showed that the study would have to be continued for another 6 yrs. Furthermore, conditional power calculations performed at this time showed no opportunity to detect a significant difference in survival. Hence, the study group decided to terminate the study. Follow-up data were collected up to October 1996. End-points were response after induction therapy, time to progression, and survival. Response and toxicity were evaluated according to WHO criteria [22]. Patients who showed disease progression at any time-point were taken off study medication but were followed-up for survival analysis. The attending physicians were free in their decision about further treatment.

**Analysis**

All original data sent by the participating centres were reviewed by one of the research group (S.O.). Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS). Differences by therapy arm for clinical characteristics, response, and toxicity were assessed by Chi-squared statistics. Time to progression and survival were compared using Kaplan Meier statistics and log rank test. A p-value of less than 0.05 was considered significant.

**Ethics**

The study protocol was approved by the Ethics Committee of the Medical Faculty, University of Innsbruck, Austria, and by the local Ethics Committees of the participating centres. Written informed consent was obtained from all patients.

**Results**

**Randomization**

The two arms were well-matched in terms of age, sex, stage and performance status. Although there were more patients with liver and CNS metastasis in the chemotherapy arm (table 1) these differences were not significant.

**Induction chemotherapy**

The median total doses of cytotoxic agents were similar in the interferon arm and chemotherapy arm (cyclophosphamide 4,800 vs 5,100 mg; doxorubicin 240 vs 240

<table>
<thead>
<tr>
<th>Table 1. Patients’ characteristics</th>
<th>Total</th>
<th>Interferon arm</th>
<th>Chemotherapy arm</th>
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</thead>
<tbody>
<tr>
<td>Patients n</td>
<td>77</td>
<td>43</td>
<td>34</td>
</tr>
<tr>
<td>Median age yrs</td>
<td>62</td>
<td>63</td>
<td>60</td>
</tr>
<tr>
<td>Males/females %</td>
<td>88/12</td>
<td>88/12</td>
<td>88/12</td>
</tr>
<tr>
<td>Karnofsky index</td>
<td>90</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Stage IIIb/IV %</td>
<td>43/57</td>
<td>42/58</td>
<td>41/59</td>
</tr>
<tr>
<td>Liver metastases %</td>
<td>30</td>
<td>26</td>
<td>35</td>
</tr>
<tr>
<td>CNS metastasis %</td>
<td>12</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Drop-out n</td>
<td>8</td>
<td>4</td>
<td>4</td>
</tr>
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CNS: central nervous system.
mg; vincristine 6.0 vs 6.0 mg; cisplatin 360 vs 360 mg; etoposide 1,470 vs 1,500 mg, respectively). The mean duration of the induction phase was 3.5 months in the IFN arm and 3.2 months in the chemotherapy arm. This slight difference (p>0.1) is almost entirely explained by the longer induction treatment protocol in the IFN arm.

Response after induction therapy

Response rates for all evaluable patients are summarized in table 2. Patients in the IFN arm had significantly higher rates of complete and partial remission (72%; 95% confidence interval (95% CI) 59–85) than those in the chemotherapy arm (44%; 95% CI 27–61; p<0.05 by Pearson Chi-squared test). Of the 77 patients, 51 completed the induction phase according to protocol (IFN arm (n=28); chemotherapy arm (n=23)), whilst the remainder (n=26) were removed from the study at an earlier time-point. Reasons included toxicity (IFN arm (n=1)); progression (IFN arm (n=6); chemotherapy arm (n=1)); refusal (IFN arm (n=4); chemotherapy arm (n=1)); death (IFN arm (n=1)); and other reasons (IFN arm (n=3); chemotherapy arm (n=1)). In the subgroup that completed the induction phase according to protocol, response rates (IFN vs chemotherapy arm) were as follows: complete remission 12 (43%) vs 5 (22%); partial remission 13 (47%) vs 9 (39%); stable disease 2 (7%) vs 3 (13%); and progression 3 (10%) vs 6 (26%). Again, more patients in the IFN arm achieved complete or partial remission than in the chemotherapy arm (p<0.05; Pearson Chi-squared test).

Maintenance therapy

From the 31 patients in the IFN arm who should have received IFN maintenance therapy, five refused further treatment or follow-up, one died suddenly after the induction phase, one was subjected to tumour resection, and two were lost from follow-up. In the remainder, maintenance IFN treatment was given for a median 12.2 weeks; the median total dose of IFN was 333 µg.

Other therapies

Radiotherapy. Nine patients in the IFN arm and four in the chemotherapy arm received thoracic radiation after induction treatment (median 42.0 vs 50.0 Gy). Among the patients who survived longer than 2 yrs, only two were irradiated, one of them as salvage therapy after local disease progression. In all the other stage IIIIB patients, radiotherapy was suspended due to early disease progression or owing to shortage in capacity at some participating centres.

Operation. One patient in the IFN arm underwent thoracic surgery for tumour resection after induction therapy.

Time to disease progression

Time to progression (as defined by the time between the first day of treatment and first documentation of progressive disease) was not significantly different between the IFN arm (7.6 months) and the chemotherapy arm (5.4 months). In the IFN arm, time to progression was 8.8 months in patients who had received maintenance therapy, and 9.0 months in those who had not.

Survival

A total of 73 patients were evaluable for survival (IFN arm (n=43); chemotherapy arm (n=30)). Four of the 77 patients were not considered evaluable because no more information had been obtained at least 6 months after the last observation. Median survival was 11.0 months (95% CI, 9.4–12.6 months) in the IFN arm and 9.0 months (95% CI, 7.7–10.3 months) in the chemotherapy arm, respectively. There was a significant survival benefit for patients in the IFN arm (p<0.02) (figure 1). Six patients in the IFN arm (14%), but none in the chemotherapy arm, survived for 2 yrs or longer. Five of these six patients presented with stage IV disease.

Toxicity

Toxicity data are summarized in table 3. During induction therapy, significantly more patients in the IFN arm than in the chemotherapy arm had febrile episodes.

<table>
<thead>
<tr>
<th>Table 2. – Response after induction: all evaluable patients (n=77)</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Complete remission</td>
</tr>
<tr>
<td>Partial remission</td>
</tr>
<tr>
<td>Stable disease</td>
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<tr>
<td>Progression</td>
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Values are presented as absolute number, and percentage in parenthesis.
Table 3. — Toxicity: patients who suffered at least one event

<table>
<thead>
<tr>
<th></th>
<th>Interferon arm (n=43)</th>
<th>Chemotherapy arm (n=34)</th>
</tr>
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<tbody>
<tr>
<td>Fever</td>
<td>26 (60)</td>
<td>9 (26)</td>
</tr>
<tr>
<td>Nausea (grade 3)*</td>
<td>8 (19)</td>
<td>5 (15)</td>
</tr>
<tr>
<td>Vomitus (grade 3)*</td>
<td>6 (14)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Alopecia (grades 3/4)</td>
<td>8 (19)</td>
<td>10 (29)</td>
</tr>
<tr>
<td>Skin rash</td>
<td>2 (5)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Granulocytopenia (grades 1/2)</td>
<td>8 (19)</td>
<td>9 (26)</td>
</tr>
<tr>
<td>Granulocytopenia (grades 3/4)</td>
<td>15 (35)</td>
<td>5 (15)</td>
</tr>
<tr>
<td>Thrombocytopenia (grades 1/2)</td>
<td>6 (14)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Thrombocytopenia (grades 3/4)</td>
<td>4 (9)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Values are presented as absolute number, and percentage in parenthesis. *: no grade 4 recorded.

(p<0.01). There were no differences in the frequency or severity of nausea, vomitus, alopecia, or skin rash. There were more grade 3/4 granulocytopenias (p<0.05) and more grade 3/4 thrombocytopenias (p<0.05) in the IFN arm than in the chemotherapy arm. During the maintenance phase, toxicity was limited to fever and moderate bone marrow suppression in the IFN arm.

Discussion

The aim of this study was to investigate, in a randomized trial, the efficacy of adjunctive IFN-α-2c in the therapy of advanced SCLC. The results show that the addition of IFN-α-2c may improve response rates and survival.

Using natural IFN-α as a single agent, Mattson and co-workers [11] obtained partial and minor responses in a small number of patients, which was considered consistent with an antitumour activity of IFN-α. However, these results could not be confirmed [12, 23]. Pezza et al. [24] administered recombinant IFN-α together with induction polychemotherapy and radiotherapy and obtained remarkably high response rates (p>0.05 complete response (CR), 32% partial response (PR)) in a phase I/II study, and yet median survival was in the usual range (11.8 months).

The only phase III trials to investigate the effects of IFN-α in SCLC were published by Mattson and co-workers [20, 25, 26]. In a three-armed study with natural IFN-α as maintenance therapy following induction chemotherapy and consolidation radiotherapy, they observed a markedly improved long-term survival in the IFN arm [25, 26]. Mattson and co-workers [20] also investigated the efficacy of adjunctive natural or recombinant IFN-α in the induction phase. However, neither adjunctive natural nor recombinant IFN-α proved superior to chemotherapy alone. To the best of our knowledge, our study is the first to show an advantage of a combined regimen both in response after induction and in survival.

The mechanism by which IFN-α acts as an antitumour agent is not precisely known. On the one hand, IFNs have a direct antiproliferative effect [7, 8] and downregulate the expression of oncogene products [27]. On the other hand, they can modulate the interaction between tumour cells and host leucocytes involved in immune defence, e.g. by enhancing natural killer cell-mediated cytotoxicity [28]. The surface expression on tumour cells of major histocompatibility complex (MHC) class I molecules, which is deficient in SCLC [29], is increased by IFN-α [30]. This might facilitate the recognition and destruction of cancer cells by cytotoxic T-lymphocytes [27, 30]. Furthermore, a loss of IFN genes on chromosome 9p can occur in all types of lung cancer [31]. and exogenous IFN-α might overcome a relative deficit of this cytokine in the tumour microenvironment.

The results of this study must be interpreted with caution. Firstly, the total number of patients investigated was low. This was due to slow patient accrual, resulting in early termination of the study. It has remained unclear as to why the participating centres randomized only about half as many patients as they had expected, so that some selection bias cannot be entirely ruled out. Secondly, the response rates, especially in the chemotherapy arm, were lower than could be expected from the literature. Again the low number of patients makes interpretation difficult. Furthermore, only patients with advanced disease were eligible for the study, and there might have been a preponderance of "variant" SCLC, responding poorly to chemotherapy. In addition, relatively low doses of cytotoxic agents had been chosen to avoid a potentiation of the myelosuppressive effect by IFN-α-2c [13]. Finally, more patients in the IFN arm received local radiotherapy, albeit in a lower median dose. The difference in survival between the two arms is heavily weighed by the six long-term survivors in the IFN arm, and only two of them were irradiated. Therefore, it seems unlikely that radiation, rather than IFN treatment, helped improve survival.

Toxicity was characterized by fever and a higher grade of myelosuppression in the IFN arm, as could have been expected. However, no major delays in treatment were observed in the IFN arm. Quality of life data were collected but have not yet been analysed due to staff shortage.

In summary, the results suggest that adjunctive interferon-α-2c may improve response rates and survival in advanced small-cell lung cancer. Due to the low number of randomized patients, the clinical relevance of these findings remains to be defined. Further clinical studies on the efficacy of interferon-α as an adjunctive and/or maintenance treatment appear to be warranted.

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References