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Original Paper

Role of Recombinant Interferon-gamma Maintenance in Responding Patients with Small Cell Lung Cancer. A Randomised Phase III Study of the EORTC Lung Cancer Cooperative Group

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This study was undertaken to determine if recombinant interferon-gamma (rIFN-γ) given every other day as maintenance therapy could prolong the survival of patients with small cell lung cancer (SCLC) who achieved a complete or nearly-complete response to induction therapy. A secondary endpoint was to assess the toxicity of alternate day doses of this treatment. One hundred and seventy seven patients in complete or nearly-complete response following chemotherapy with or without thoracic radiotherapy were studied. Patients were randomised to receive either rIFN-γ 4 million units (0.2 mg) subcutaneously every other day for 4 months or observation. One hundred and twenty of the 127 registered patients were eligible; 59 patients received IFN and 61 patients without maintenance therapy were followed. Alternate day IFN was reasonably well tolerated by the majority of patients, but in 12% substantial non-haematological toxicity (including flu-like syndrome) occurred. One of 3 patients with pneumonitis died after having received 3.6 mg IFN. The median survival time from the date of randomisation was 8.9 months for the IFN arm and 9.9 months for the observation arm. rIFN-γ at the dose and schedule used in this study failed to prolong response duration and survival in SCLC patients in complete or nearly-complete response. The toxicity seen with every other day doses of IFN was less than that reported with daily dosing. The hypothesis that this agent may increase the deleterious effects of radiation on normal lung tissue was supported by the development of pneumonitis in 3 cases of whom 1 had a fatal outcome. The results do not warrant further studies with rIFN-γ on maintaining response in SCLC. © **1997 Elsevier Science Ltd.**

Key words: small cell lung cancer, interferon type II, rIFN-γ, maintenance therapy
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INTRODUCTION

SMALL CELL lung cancer (SCLC) distinguishes itself from other types of lung cancer by its more aggressive clinical course in the absence of treatment and its greater responsiveness to chemotherapy and thoracic irradiation [1]. Although combination chemotherapy has had a substantial

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impact on the management of patients with SCLC, little improvement in the overall results of treatment has been observed since the beginning of the 1980s. Neither dose intensification nor alternating combination chemotherapy have convincingly improved survival [2, 3].

In 1988 following the first indications that maintenance chemotherapy did not offer a better chance of cure than short-term chemotherapy [4], the EORTC Lung Cancer Cooperative Group decided to start investigating the possibility of prolonging remission and/or survival with biological response modifiers. At that time recombinant technology had provided the opportunity to test interferons on a large scale. Interferons, originally recognised by their ability to induce resistance to viral infection, belong to a family of inducible secreted proteins, which regulate cellular proliferation and differentiation as well as immune function via complex interactions [5]. They interact with target cells by binding to specific cell surface receptors and also exert several antitumour effects involving both direct and indirect action on tumour cells [6, 7].

Mattson and associates [8] conducted the first randomised study in SCLC patients that used interferon as maintenance therapy. SCLC patients who objectively responded to chemotherapy and radiotherapy were randomised to receive no maintenance therapy, chemotherapy maintenance or low-dose natural interferon-alpha (nIFN-α) for 6 months. Although there were no overall differences in survival, a subgroup analysis revealed a survival advantage ($P = 0.02$) for those patients with limited-stage disease who received maintenance IFN. These results prompted the investigation of recombinant IFN-gamma (rIFN-γ) as this type of interferon was assumed to possess even stronger immunomodulatory effects than IFN-α and also had shown specific activity against SCLC in cell culture [9–11].

The dose range of rIFN-γ used in the present study in SCLC patients in complete or nearly complete response (CR) was based on data from the biological response modifiers programme of the National Cancer Institute [12]. The aim was to accrue a total of 200 SCLC patients. However, the premature closure of a similar study by the NCCTG reported by Jett and associates [13], after an interim analysis suggesting inferior survival of patients on rIFN-γ maintenance, significantly affected the accrual rate of this study, which as a consequence was terminated after inclusion of 127 patients. Here we report the results obtained in these 127 SCLC patients in response after chemo- and radiotherapy.

PATIENTS AND METHODS

To be entered into this study, patients with histologically or cytologically diagnosed SCLC had to have a documented CR or nearly CR on chemotherapy with or without radiotherapy, an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1, and adequate haematological, cardiac, renal and liver functions. A nearly CR was defined as the roentgenological persistence of subtle lesions in the area of previous disease that could not be diagnosed as residual disease. Informed consent and expected cooperation with protocol treatment and follow-up were required. Patients with serious active infections were excluded.

There were no specific requirements for the chemotherapy employed. All patients included had to have received chemotherapy according to current active protocols. Postchemotherapy restaging procedures consisted of a history and physical examination (including bronchoscopy), complete blood cell count, chemistry profile, chest X-ray, chest computer tomography (CT) scan and bronchoscopy. Bone scans, abdominal ultrasounds or CT scans were repeated only if prechemotherapy investigations had shown abnormalities.

Patients, who were judged to be in CR or nearly CR on the basis of re-staging examinations, were eligible for randomisation to this protocol treatment with rIFN-γ or observation only. At randomisation patients were stratified by the extent of disease (limited versus extensive disease) and performance status (0/1 versus 2/3) at initial (prechemotherapy) presentation. Patients were randomised as soon as possible after re-staging and not later than 8 weeks from the last day of chemo- or radiotherapy.

Treatment programme

Patients were randomised by the EORTC Data Center and assigned to either observation only or to treatment with rIFN-γ (Boehringer Ingelheim, Alkmaar, The Netherlands/ Genentech, San Francisco, U.S.A.). As prolonged ($\pm$48 hr) enhancement of immunological function was observed after a subcutaneous dose of 0.1 mg/m^2 rIFN-γ (approximately 0.2 mg total dose), a dose of 0.2 mg every other day was chosen [11]. Patients and/or family members were instructed in the appropriate technique for subcutaneous injections. Acetaminophen 500 mg orally was permitted to minimise febrile reactions if needed. Other medications such as aspirin, other non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids were not permitted.

Patients randomised to receive rIFN-γ were monitored every 2 weeks for the first two visits and then monthly until completion of the 4 months period of therapy. During the observation period, patients were monitored until there was evidence of disease progression. At follow-up all patients had a history, physical examination, complete blood cell count, serum chemistry and chest X-ray. Additional scans/ ultrasounds were obtained only if indicated by clinical symptoms. Patients experiencing mild (grade I) toxicity from rIFN-γ therapy were continued on treatment with no change in dosage. For patients who suffered grade II or III toxicity, the rIFN-γ dose was withheld until the return to $\leq$grade I, at which point the patient resumed treatment at 50% of the dose. In the case of grade III neurotoxicity (polyneuropathy), rIFN-γ therapy was permanently discontinued.

Statistical considerations

The main endpoint of the study was survival. The expected 2-year survival in the standard arm was 20% (based on EORTC trial 08825) [4]. An increase to 35% in the 2-year survival in the gamma-IFN arm was considered to be clinically worthwhile. In order to detect such a benefit (with a power of 80% using a two-sided significance level of 5%), 100 patients should have been entered in each arm and followed for an average of 2 years.

Randomisation was carried out using the minimisation technique [14], stratifying patients according to their institution and performance status before prior chemotherapy (0–1 versus 2–3) and extent of disease before prior chemotherapy (limited versus extensive).

Duration of survival and time to progression (the time interval between the date of randomisation and the date of disease progression) curves were estimated using the Kaplan–Meier technique [15] and a two-sided logrank test [16] was used for treatment comparisons. In order to adjust for possible prognostic factors, the Cox proportional hazards regression model [17] was used.

The main analysis was performed on all randomised patients according to the 'intent-to-treat' principle. For comparative reasons, a second analysis was performed on all eligible patients.

RESULTS

Between April 1989 and September 1993, 127 patients were entered into EORTC trial 0883, 65 patients were randomised to treatment with rIFN-γ and 62 patients were randomised to observation only. At review 7 patients were judged ineligible, 6 in the IFN-γ arm and 1 in the observation arm. Six of them were found to be incorrectly restaged as complete or nearly complete responders. In one case no follow-up information was obtained. Demographic and baseline features are given in Table 1. The groups were comparable with respect to the interval from the date of diagnosis to the time of entry in the trial. There was a good balance between the two arms for stratification factors as well as for stage, gender and type of previous chemotherapy; 67–68% had limited disease and 32–33% had extensive disease, and in both arms 1 patient had prior brain metastases. 88% of the patients had a performance score of 0/1 at the start of prior chemotherapy. Combination chemotherapy was the only treatment before entering this protocol in 46% in the rIFN-γ arm and in 43% of the patients in the observation arm. For limited disease patients, 30 patients (75%) received both chemotherapy and radiotherapy in the rIFN-γ arm and 33 patients (80%) in the observation arm.

Compliance and toxicity

Four eligible patients in the rIFN-γ arm were excluded from the analysis of toxicity. One patient refused interferon treatment immediately after randomisation. Another patient could not start protocol treatment as he was hospitalised for a suspect radiation-induced pneumonitis. Two patients stopped protocol treatment within 10 days, one of them showed progression after having received 0.4 mg IFN, the other discontinued after a total dose of 0.6 mg IFN. The analysis of toxicity was based on 55 patients in the rIFN-γ arm and 61 patients in the observation arm. The total dose of rIFN-γ administered is shown in Table 2, and the reasons for stopping protocol treatment are given in Table 3.

Haematological toxicity mainly consisted of mild leucopenia. Thrombocytopenia or anaemia were not noted. No cardiac, hepatic, gastrointestinal or renal toxicities of rIFN-γ were noticed. Flu-like symptoms, accompanied by (a slight) alteration of mental status, fatigue and headache were noted in 69% of patients in the rIFN-γ arm. Toxicity causing termination of treatment was noted in 7 cases. Four of these patients suffered from a severe fever/flu-like syndrome upon IFN injection. In 1 case there was grade III polyneuropathy and another patient was advised to stop treatment because of leucopenia grade II. A third patient, who received chemotherapy followed by radiotherapy and started rIFN-γ treatment 30 days after completion of RT, developed severe

Table 1. Patient and tumour characteristics by treatment arm

Characteristic	Gamma IFN $n = 59$	(%)	Observation $n = 61$	(%)
Sex				
Female	16	(27)	17	(28)
Male	43	(73)	44	(72)
Extent of disease*				
Limited	40	(68)	41	(67)
Extensive	19	(32)	20	(33)
WHO performance status*				
0	22	(37)	20	(33)
1	31	(53)	34	(56)
2	3	(5)	7	(11)
3	3	(5)	0	(0)
Prior chemotherapy				
CDE†	39	(66)	46	(75)
CDE alternating with platinum combination	6	(10)	3	(5)
Platinum combination alone	9	(15)	10	(16)
Other	5	(8)	2	(3)
Prior radiotherapy	30	(51)	34	(56)
Prior surgery	4	(7)	3	(5)
Response achieved prior to randomisation				
Complete	42	(71)	39	(64)
Nearly complete	17	(29)	22	(36)
WHO performance status‡				
0	37	(63)	33	(54)
1	21	(36)	28	(46)
unspecified	1	(2)	0	(0)
Interval (days) between dates of CR and randomisation	11 (median)		10 (median)	

*Before initiation of chemotherapy. †Cyclophosphamide, doxorubicin, etoposide. ‡At randomisation.

Table 2. Total dose of rIFN-γ administered

Total dose (mg)	$n = 59$	(%)
0	2*	(3)
<1	5	(8)
1–5	18	(31)
6–10	16	(27)
11–20	17	(29)
30	1	(2)

*1 patient refused treatment after randomisation. Another patient suffering from pneumonitis could not start treatment.

pneumonitis after 3.6 mg IFN and eventually died. Autopsy revealed a congested lung with hyaline membranes and extensive fibrotic changes.

Survival and progression-free survival

At the time of the analysis, 110 patients had died (56 in the rIFN-γ arm and 54 in the observation arm). Median duration of survival (from the date of randomisation) was 8.9 and 9.9 months, respectively ($P = 0.890$, Figure 1). The 1- and 2-year survival estimates in the rIFN-γ arm were 33% (95% CI: 21–45%) and 17% (95% CI: 7–27%), respectively. The corresponding figures in the observation arm were 42% (95% CI: 30–54%) and 14% (95% CI: 5–23%), respectively. The median survival per treatment arm according to disease extent at randomisation was for limited disease 10.4 months in the rIFN-γ arm and 11.1 months in the observation arm. For extensive disease the figures were 6.5 months in the rIFN-γ arm and 9.4 months in the observation arm. These apparent differences were not statistically

*Table 3. Reasons for stopping treatment**

Reason	Gamma IFN $n = 59$	(%)	Observation $n = 61$	(%)
End of protocol period	17	(29)	25	(41)
Progression or recurrence	29	(49)	35	(57)
Dose received (in mg)				
<1	2			
1–5	10			
6–13	17			
Excessive toxicity	7†	(12)	0	
Refusal	2	(3)	0	
Dose received (in mg)				
0	1			
5	1			
Radiation pneumonitis	3	(5)	0	
Other reason	1‡	(2)	1§	(2)

*Only for IFN arm. †Respiratory distress after 3.6 mg of rIFN-γ (1 patient), polyneuropathy grade III (1 patient), leucopenia grade II (1 patient), fever/flu-like syndrome (4 patients). ‡Expired medication. §Regular follow-up not feasible (nursing home).

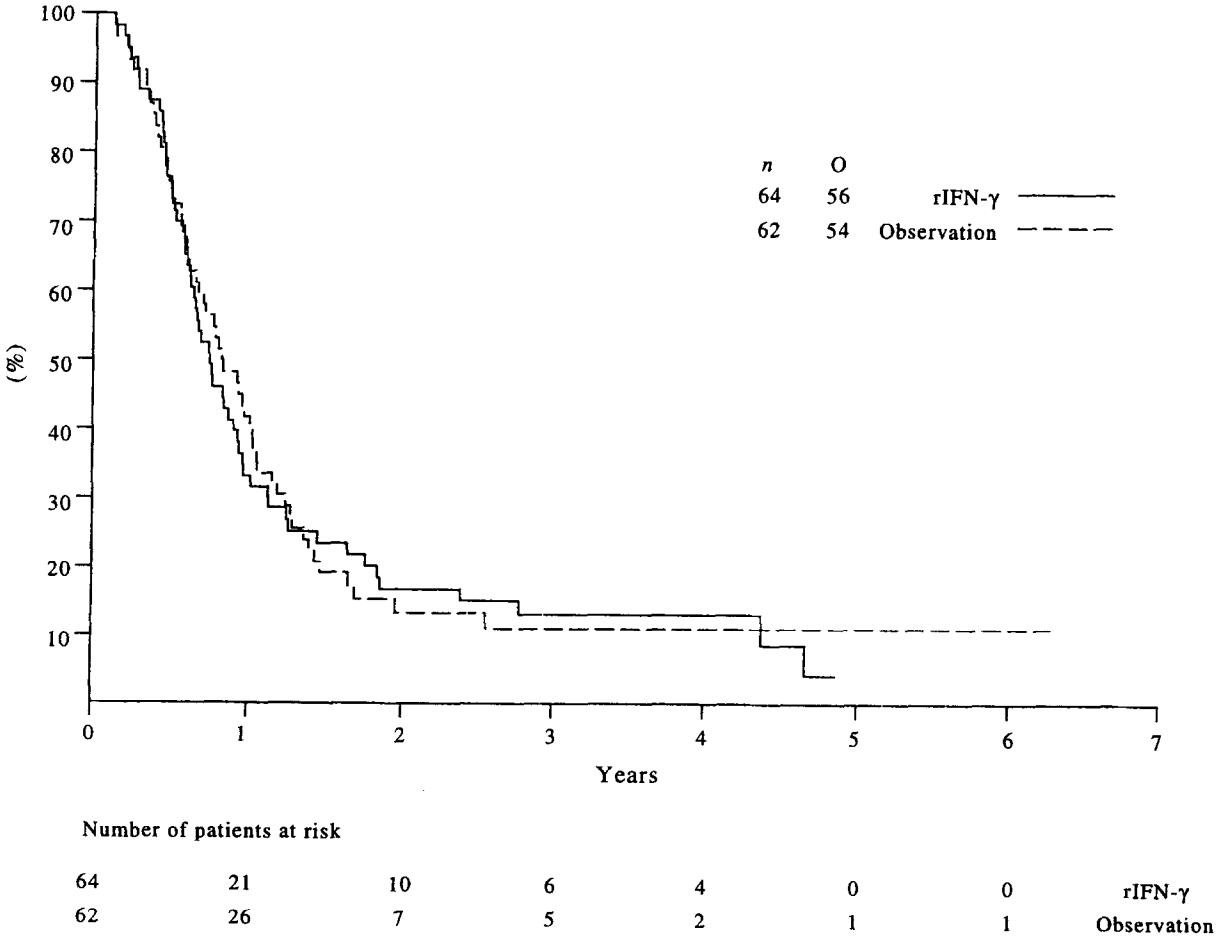

Figure 1. Overall survival curve from date of randomisation for patients randomised to receive rIFN-γ or observation only.

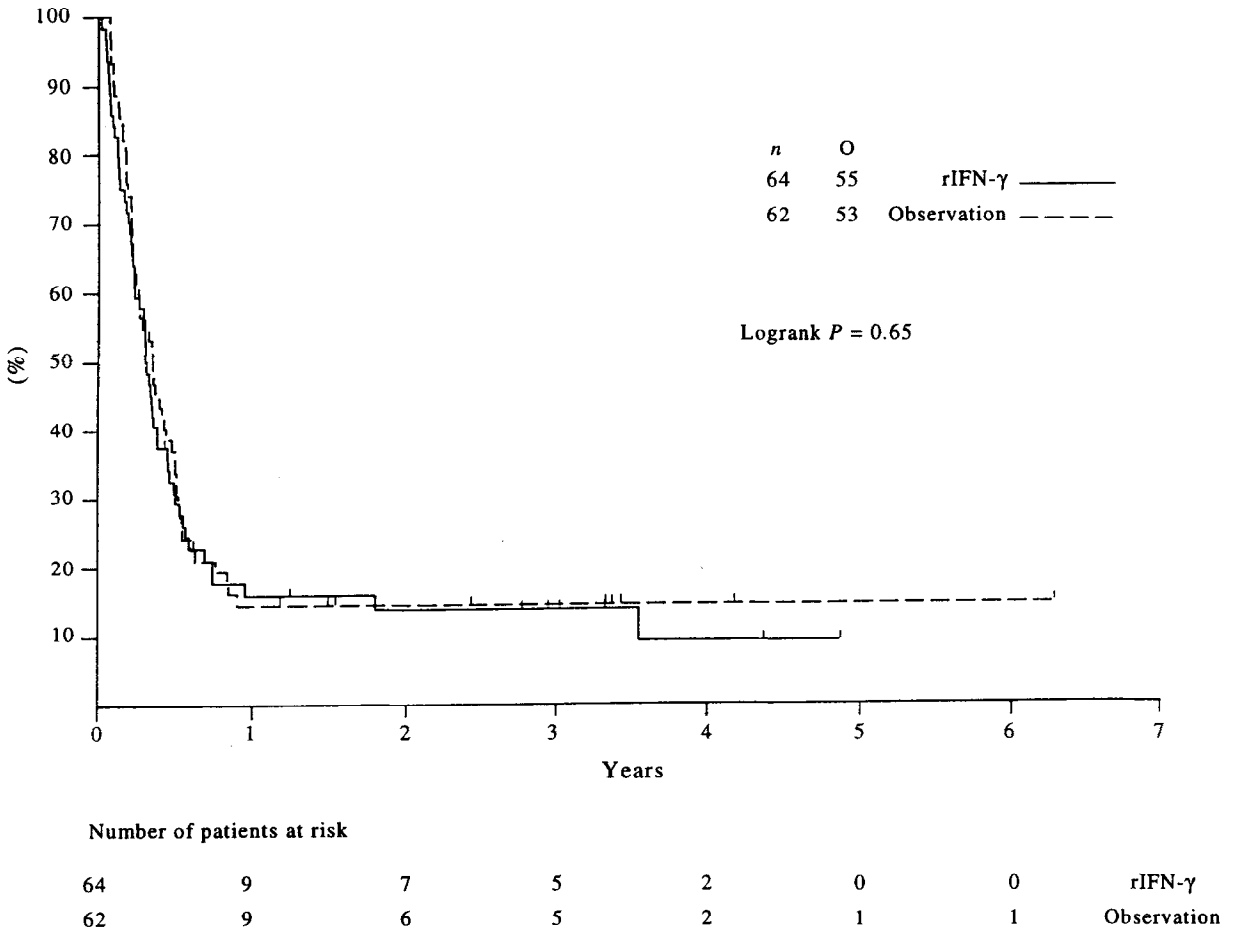

Figure 2. Time-to-progression curve from date of randomisation for patients randomised to receive rIFN-γ or observation only.

significant. A multivariate Cox model for survival was used to test the treatment effect after adjustment for possible prognostic factors (age, sex, response achieved at randomisation (CR versus nearly CR), performance status (0 versus 1), the treatment was still not significant (relative risk of 1.03, 95% confidence interval: 1.70–1.51, $P = 0.905$) and none of these factors was found to influence survival significantly. Recurrence was reported for 108 patients (55 in the rIFN-γ and 53 in the observation arm). The median time to progression was 3.7 months and 4.2 months, respectively ($P = 0.652$, Figure 2). These results did not substantially change when analyses were performed on all eligible patients ($P = 0.681$ for progression and 0.879 for survival).

DISCUSSION

Despite high response rates to chemotherapy, the long-term survival and cure rate of SCLC are disappointingly low. It is clear that more active drugs and new treatment strategies are needed. In previous studies by us and other groups it has been concluded that maintenance chemotherapy, although slightly prolonging progression-free survival, failed to have a positive impact on overall survival [18–22]. Furthermore, maintenance chemotherapy is often associated with excess toxicity and a poorer quality of life. Based on these observations it became standard practice to treat patients with SCLC with only 5–6 courses of chemotherapy.

At the end of the 1980s, recombinant technology made available several types of interferons in sufficient quantities for clinical studies. It was theorised that these glycoproteins with antiviral, antiproliferative and immunomodulatory effects would exert a maximal antitumour effect in patients with minimal residual disease. We made the choice of IFN-γ as a maintenance drug considering at least three properties that could be of benefit in the treatment of minimal residual disease: stimulation of natural killer cell-mediated cytotoxicity, activation of macrophages and enhancement of histocompatibility antigen (HLA) class I and II antigen expression [11, 23].

Unfortunately, like the final outcome of the study by Jett and associates [24], our data could not confirm the encouraging results obtained by Mattson and associates [25], with nIFN-α, with no beneficial effect of rIFN-γ observed on the survival of SCLC patients in complete or nearly-complete response. However, a detrimental effect of rIFN-γ as suggested by the interim analysis of Jett and associates [13], was not observed. Recently, Kelly and associates (SWOG) also reported negative results using rIFN-α-2a maintenance in limited disease SCLC patients in remission after chemotherapy [26] (Table 4). The toxicities in this study (using IFN-α-2a 3×10^6 U 3 times per week) were significant and might also have contributed to the end result, as 43 of the 64 randomised patients discontinued protocol treatment due to intolerable side-effects. In our

Table 4. IFN maintenance studies in SCLC (overview)

Authors	Mattson and associates [25]			Jett and associates [24]		Kelly and associates [26]		Current study	
Induction therapy	4 × CAV + 55 Gy chest RT (split course)			2 × PE 4 × CAV, 37.5 Gy chest RT		Concurrent PE (3 cycles) + 45 Gy chest RT, followed by 3 PE at reduced dosage, ±GM-CSF		71% CDE (5–6 courses), 24% platinum-containing regimens (4–6 courses), 54% chest RT	
Response	CR + PR			CR		CR + PR		CR + nearly CR	
Maintenance therapy	rIFN-α	CAP*	Observation	rIFN-γ	Observation	rIFN-α 2a	Observation	rIFN-γ	Observation
No. of subjects (eligible)	91	59*	87	51	49	64	68	59	61
Gender (male %)	79	80	74	47	51	58	54	73	72
Stage (LD %)	62	56	64	76	86	100	100	68	67
PS (0–1) %	32	36	41	84	94	92	97	90	89
IFN schedule	3×10^6 U/day i.m. 5 times per week (1 month) followed by 6×10^6, 3 × week (5 months)			0.2 mg (4×10^6 U) s.c. daily for 6 months		3×10^6 U (3 × week) increased to max 9×10^6 U (3 × week) for 2 years		0.2 mg (4×10^6 U) s.c. every other day for 6 months	
No. subjects on IFN 'duration' of maintenance	64 pts. 26 pts. continued 6 months 48 pts. continued 3 months			50 pts. 18 pts. completed 6 months 9 pts. discontinued treatment, 11 pts. early progression		62 pts. 1 pt. completed 2 years 67% discontinued due to intolerable side-effects		57 pts. 17 pts. completed 4 months 7 pts. stopped because of excessive toxicity	
Toxicity	NR†			29% grade III		4 pts. grade IV toxicity 19 pts. (30%) grade III toxicity 2 pts. pneumonitis		1 pt. fatal pneumonitis after chemo and RT and 3.6 mg of IFN	
Median survival (months)‡	11	10	10	13.3	18.8	13	16	8.9	9.9

CAV, cyclophosphamide, doxorubicin, vincristine; CAP, cyclophosphamide, doxorubicin, cisplatin; PE, cisplatin, etoposide; CDE, cyclophosphamide, doxorubicin, etoposide; CR, complete response; PR, partial response. *CAP arm discontinued halfway study. †NR, not reported. ‡Counted from date of randomisation

study with 0.2 mg rIFN-γ (4×10^6 U) every other day, 7 of the 65 randomised patients stopped protocol treatment due to toxicity. In the NCCTG experience, with the same dose administered every day and a measurable effect on immune response [27], 5 of the 51 patients refused rIFN-γ due to unacceptable side-effects, while in 12 patients dose reduction was necessary according to protocol guidelines. In comparing the toxicities of these studies, it is clear that alternate day dosing of rIFN-γ (0.2 mg) is reasonably well tolerated with a substantially lower percentage of side-effects than with rIFN-α-2a 3 times per week or daily rIFN-γ. It is noteworthy, however, that 1 patient in our study receiving rIFN-γ died as a consequence of a severe pneumonitis. In this case IFN therapy was initiated shortly after completion of a chest irradiation and we suspect that sensitisation by IFN-γ of normal lung tissue to the effects of radiation might have played a role, as has recently been demonstrated by an NCCTG study [28].

Interestingly, when rIFN-α was compared with the combination rIFN-α + rIFN-γ in patients with renal cell cancer, the combination of interferons elicited approximately the same intensity of side-effects as single-agent rIFN-α [29]. However, in terms of survival, a negative effect of the addition of rIFN-γ could not be excluded. It may thus be concluded that although the toxicity seen in IFN-γ is less than that of IFN-α, a significant activity of IFN-γ against residual cancer is highly unlikely. Lack of significant activity of rIFN-γ had already been suspected on the basis of phase II experience in SCLC [30, 31].

On reviewing the data of IFN maintenance studies (Table 4), there is one issue that may have contributed to the lack of effect of interferons in maintaining response in SCLC: a substantial proportion of the test populations, notwithstanding the intention of long-term therapy, had very limited exposure to IFN due to either toxicity or a high percentage of patients relapsing shortly after completion of chemotherapy and radiotherapy. However, it is clear that rIFN-γ, after a major response upon induction therapy as prescribed in our study, cannot be recommended. Despite this negative conclusion it may still be worthwhile to investigate the role of IFN in a condition where resistance to therapy most likely plays a less prominent role, e.g. early malignant changes of the respiratory epithelium [32].

Comparing the survival data of our study with those of Jett and associates and Kelly and associates, there appears to be a difference in median and long-term survival in favour of the two American studies. In the SWOG study, involving only limited disease patients after an objective (not necessarily complete) response, median survival figures of 13 and 16 months were recorded for the IFN-α and control arm, respectively. In the NCCTG study with similar selection criteria as our study, overall survival figures were in the same range, higher than 8.9 and 9.9 months of the respective IFN and control arms in our study.

An explanation for these differences may be found in the higher percentage of extensive disease patients in our study (32% EORTC versus 22% NCCTG versus 0% SWOG). The fact that only 53% of the current study population had received radiotherapy to the chest and that the chemotherapy employed in this study included a platinum compound in only 23% of the cases may also have contributed.

This study once more confirms the tendency of SCLC to recur quickly after a major response to chemotherapy even in the very best category of patients. Hopefully new active drugs and new combinations given according to their pharmacokinetic properties will help to improve treatment results.

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APPENDIX

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