EORTC (30885) randomised phase III study with recombinant interferon alpha and recombinant interferon alpha and gamma in patients with advanced renal cell carcinoma

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Summary In the treatment of renal cell carcinoma both complete (CRs) and partial remissions (PRs) have been obtained using recombinant (r) interferon alpha (IFN-a), with response rates ranging from 0 to 31% (mean 16%). IFN-γ is a potent immunostimulating agent, but the clinical experience of its use is limited and results are conflicting. In a phase II study with the combination of rIFN-a2c (Boehringer Ingelheim) and rIFN-γ (Genentech, supplied by Boehringer Ingelheim) in 31 eligible patients, a response rate of 25% was recorded. Based on this observation a randomised phase III study was initiated to investigate the possible advantage of the addition rIFN-γ to rIFN-a2c treatment. Treatment consisted of rIFN-a2c 30 μg m⁻² = 10 x 10⁶ IU m⁻² s.c. twice weekly in arm A and the same dose of rIFN-a combined with rIFN-γ 100 μg m⁻² = 2 x 10⁶ IU m⁻² in arm B. Eligibility criteria included documented progression of disease; patients with bone lesions only and overt central nervous system metastases were excluded. Between November 1988 and September 1990, 102 patients were entered into the study. An interim analysis showed a response in 7/53 (13%) patients (two CRs and five PRs) in the rIFN-a2c monotherapy arm and in 2/45 (4%) (one CR and one PR) patients in the combination arm. This difference was not statistically significant (P = 0.17). The probability of missing an eventual 10% advantage for the combination is 0.001. The numbers are insufficient to rule out a negative effect of the addition of rIFN-γ. The dose intensity of IFN-a2c for the two treatment arms was the same. The addition of rIFN-γ does not improve the response rate of rIFN-a2c monotherapy. A possible detrimental effect cannot be excluded.

Keywords: renal cell carcinoma; interferon alpha; interferon gamma.

Patients with renal cell carcinoma (RCC) currently have few therapeutic options once the disease has become metastatic. Approximately 25% of such patients have metastatic disease at the time of first presentation. The median survival for these patients is independent of treatment, 6–12 months (De Forges et al., 1988). Spontaneous regression of metastases after tumour nephrectomy occurs in less than 1% (Montie, 1977). Treatment with hormones and chemotherapy, both single agent and combination, has no proven impact on survival (Harris et al., 1983; Yagoda and Bander, 1989). Several forms of immunotherapy have been applied, resulting in a limited number of sometimes durable responses (McCune, 1983). Interferon-alpha (IFN-α) is most extensively used in the treatment of advanced RCC, both the natural and recombinant(r) forms. Most studies have provided evidence for modest but reproducible anti-tumour activity in advanced RCC (Goldstein and Laslo, 1986; Krown, 1987; Sarna et al., 1987; Muss, 1988; Buzaud and Todo, 1989; Horoszewski and Murphy, 1989). The response rates recorded from adequate trials (i.e. more than 20 eligible patients and a dose of IFN-α of more than 3 x 10⁶ U day⁻¹, n = 431) vary from 5 to 26% (mean 17%; 2% CR and 15% PR).

Experience with rIFN-γ in renal cell carcinoma is limited and, with a few exceptions, disappointing (Rinhardt et al., 1986; Quesada et al., 1987; Garnick et al., 1988; Otto et al., 1988; Aulitzky et al., 1989; Bruntsch et al., 1990). Little information is available about the optimal dose, schedule and route of IFN-γ administration.

Modification of the host response is frequently restricted to a narrow dose range, and in a recent study optimal modulation by rIFN-γ has been found in the low dose range (100 μg m⁻²) (Maluish et al., 1988). Against this background, the findings of Aulitzky et al. (1989) are interesting. They observed a 30% response rate (two CRs, four PRs) in 16 patients treated with 100 μg IFN-γ (Genentech) s.c. once a week.

The combination of IFN-α and IFN-γ has been explored on the basis of in vitro observations indicating a synergism between rIFN-γ and rIFN-α (Czarniecki et al., 1984; Hubbell et al., 1987). The results published so far are, however, disappointing (Kurzrock et al., 1986; Foon et al., 1988; Quesada et al., 1988; Ernstoff et al., 1990). De Mulder and co-workers (Geboers et al., 1988; De Mulder et al., 1990) studied the efficacy of the combination of an escalating dose rIFN-α₂c (6 μg m⁻² = 2 x 10⁶ U m⁻² starting dose) and a fixed low dose of rIFN-γ (100 μg m⁻² = 2 x 10⁶ m⁻²) twice weekly subcutaneously in patients with advanced progressive renal cell carcinoma. The overall response rate was 26% (two CRs, six PRs). The maximal tolerated dose of IFN-α₂c was 30 μg m⁻² (6–36 μg m⁻²). The feasibility and efficacy of this approach was proven in the treatment of a second cohort of patients (De Mulder et al., 1991). In view of these data, an EORTC randomised study was initiated to determine if the addition of rIFN-γ has any impact on the response rate and survival of patients with advanced metastatic renal cell carcinoma.

Patients and methods

Trial design

The study was designed as a randomised phase III trial with an interim analysis planned after data for 40 eligible patients...
were available in each arm in order to ensure that continu-

ation of the trial was ethical. After checking all eligibility
criteria, the randomisation was centrally performed at the
EORTC Data Center. Patients were stratified according to
institution and performance status. The study was performed
according to good clinical practice guidelines, which included
the verification of all items given on the forms with the
source documents. The main end points of the study were the
comparison of the two treatments arms regarding response
rate, time to response, response duration, survival and
tolerance.

Patient population
Patients with histologically proven renal cell carcinoma with
metastatic measurable or evaluable disease were considered
for the study if they met the following criteria: age 18–75
years; no prior chemo- or immunotherapy; prior hor-
monal treatment was allowed; there should have been proven
progression, especially after a recent nephrectomy; World
Health Organization (WHO) performance status 0–1; ade-
quate haematological status, renal and liver function; normal
serum calcium level; no concurrent serious medical illness
(acute infections, significant cardiac disease) or second
malignancies except adequately treated basal cell carcinoma
of the skin or cone biopsied carcinoma in situ of the cervix;
no history of seizure disorders or signs of central nervous
system metastases; life expectancy of at least 3 months;
absence of a lipoprotein disorder. Concomitant medication
with corticosteroids or vasodilators was not allowed. All
patients gave their written or witnessed informed consent.

Treatment regimen
rIFN-α2c and rIFN-γ (Genentech) were supplied by Boe-
hringe Ingelheim (Alkmaar, The Netherlands) and provided
as a sterile lyophilised powder. The powder contained 15 μg
of IFN-α2c with a degree of purity of >98% and a specific
activity of 4 × 10⁹ IU μg⁻¹ based on the NIH IFN-α
standard G03-990-527 for rIFN-α or 150 μg of IFN-γ
with a specific activity of 2 × 10⁶ IU mg⁻¹ protein, based on the
NIH IFN-γ standard Gg23-901-350. The freeze-dried prepara-
tions were reconstituted with 1 ml of sterile water immedi-
extly before use to yield rIFN-α2c and rIFN-γ concentrations
of 5 × 10⁶ IU ml⁻¹ and 10 × 10⁶ IU ml⁻¹ respectively.

Injections were given subcutaneously twice a week on an
out-patient basis, although it was recommended that the first
injection be given during a brief stay in hospital. Treatment
arm A consisted of rIFN-α2c monotherapy and arm B con-
sisted of the same dose of rIFN-α2c plus rIFN-γ. rIFN-γ was
given 3 h before the rIFN-α2c injection be given during a brief stay in hospital. Treatment
arm was given at a dose of 30 μg m⁻² (10 x 10⁶ IU m⁻²). In arm
in the case of WHO grade III–IV toxicity, treatment was to be continued with a reduction of the dose of rIFN-α2c of
6 μg m⁻². If a dose reduction resulted in a dose below
12 μg m⁻² the patient went off study. In case of grade II
haematological toxicity, this was followed every 2 weeks until
stabilisation on an IFN-α2c dose of 6 μg m⁻².

Acetaminophen (500 mg) was routinely prescribed to
alleviate side-effects. This treatment was started 4 h before
the IFN injection and continued for 24–48 h thereafter.

Pretreatment and follow-up examinations
Pre-study evaluations included full medical history and
physical examination, tumour measurements, electrocardio-
gram, chest radiograph, white blood cell count, platelets
and a complete chemistry profile. Four-weekly monitoring in-
cluded side-effects according to the WHO grading system,
haematological status, urine analyses and biochemical
measures: creatinine, alkaline phosphatase, aspartate amino-
transferase, alanine aminotransferase, lactate dehydrogenase,
**Table I** Patient characteristics at entry

|                  | IFN-α | IFN-α + IFN-γ |
|------------------|-------|---------------|
| No. of patients  | 54    | 48            |
| Not eligible     | 3     | 3             |
| Male:female      | 37:17 | 32:16         |
| Median age       | 55 (27-75) | 58 (32-74)   |

**Performance status**

| WHO 0          | 20a   | 23          |
| WHO 1          | 33    | 25          |

**Prior treatment** (n = 98)

|                     | Nephrectomy | No nephrectomy | Radiotherapy | Hormonal treatment |
|---------------------|-------------|----------------|--------------|--------------------|
| Neutrophil         | 42          | 38             | 7            | 1                  |

**Site of disease**

| Site of disease | Lungs only | Lungs + primary | Lungs + nodes | Lungs + liver | Lungs + others | Liver + others |
|-----------------|------------|-----------------|---------------|--------------|---------------|---------------|
| Number of sites | 1          | 14              | 4             | 3            | 3             | 5             |
| Number of sites | 2          | 17              | 4             | 3            | 3             | 3             |
| Number of sites | 3-6        | 12              | 3             | 2            | 3             | 2             |
| Number of sites | >5         | 0               | 1             | 0            | 1             | 0             |

Not evaluable for response 6 7

*Missing information for one patient.

**Treatment efficacy**

Considering all eligible patients (98) entered into the trial, the response rates were as follows: rIFN-α monotherapy, one CR, no pathologic CR, five PRs and 19 no change (NC), overall 13%; rIFN-α + rIFN-γ one pathologic CR, one PR and 19 NC, overall 4% (Table II). This difference was not statistically significant at \( P = 0.17 \) in favour of arm A. If a relevant difference in favour of the combination arm were 10% and the expected response on the monotherapy were 15%, the probability of missing this difference with the observed results would be 0.001. Although the difference was not statistically significant, the numbers are inadequate to show true equivalence or to exclude a potential negative effect of the addition of interferon-γ, however this was not the purpose of our study. A mixed response was seen in four out of 53 patients in arm A and three out of 45 in arm B. The median time to response among responders was 114 days (range 59-301 days) and the median response duration was 60 weeks, with seven of the nine responders having progressed. Based on an average follow-up of 1 year, the overall median survival was 43 weeks in arm A and 34 weeks in arm B (\( P = 0.73 \) (Figure 1). The time to progression is given in Figure 2. When the patients with their primary in situ are excluded, the observed response rate was 7/42 (17%) for treatment arm A and 2/38 (5%) for arm B. The characteristics of all responding patients are shown in Table III. Six out of nine responded in the lungs, however only in two patients was this the only site of disease. In two patients concomitant metastases in the liver disappeared during therapy. The sites with unmeasurable disease remained clinically unchanged. Two patients had cytological proof of renal cell carcinoma in the enlarged node prior to the start of treatment. After discontinuation of treatment lymph node dissection was performed. Pathological examination revealed no tumour and the patients are therefore considered as having a pathologic CR.

One possible explanation for the lack of response in the combination arm could be a difference in the dose intensity of rIFN-α in the two groups. However, dose intensity, dose reductions and delays were similar in the two arms. In both arms 90% of the patients received 100% of the intended dose of rIFN-α.

**Table II** Response to treatment in eligible patients

|                  | rIFN-α       | rIFN-α + IFN-γ |
|------------------|--------------|---------------|
| CR               | 1            | 0             |
| pCR              | 1            | 1             |
| PR               | 5            | 4             |
| SD               | 19           | 19            |
| PD               | 22           | 20            |
| Early death      | 2            | 3             |
| Unknown          | 3            | 1             |
| Total            | 53           | 45            |

Response rate 13% 4% (\( P = 0.17 \))

There were four mixed responses on monotherapy and three mixed responses on the combination which are included in the Table as PD.

**Figure 1** Time to progression.

**Figure 2** Duration of survival.

**Toxicity**

Observed grade II and III toxicity is given in Table IV. Side-effects were those known to be associated with interferon treatment. The vast majority of the patients developed fever, anorexia, fatigue and to a lesser extent flu-like symptoms. There was no difference between the two treatment groups. One patient developed a WHO grade III thrombocytopenia, but fully recovered after discontinuation of treatment. The white blood count (WBC) was only marginally influenced, although in the combination arm three patients developed reversible WHO grade III leukocytopenia.

**Discussion**

There is no doubt that interferons can induce responses in advanced renal cell carcinoma. The response percentage...
response rate is 17%, which is consistent with the range observed in the literature. One should realise that these results were obtained with a relatively low dose of IFN-α (10 x 10^6 IU m^-2) and a twice-weekly schedule, again an indication that the regimen is not critical and that IFN-α given above a certain threshold is able to induce responses in sensitive tumours. A remarkable finding was that in two patients an objective response in the liver was seen.

The main purpose of the study was to study the relevance of the addition of IFN-γ, which was based both on laboratory observations as well as on the results of earlier studies. The results were very disappointing because only in two patients (4%) was an objective response observed and the study, initially planned as a randomised phase III study, was stopped after an interim analysis. As indicated before, the probability of obtaining these results if a difference of 10% in favour of the combination was actually present is extremely low. Equivalence in outcome or even the inverse outcome, i.e. a potential adverse effect of the combination, cannot be excluded with adequate power in view of the numbers involved, but this was not the purpose of the study. There is no satisfactory explanation for this result. Patient characteristics of the two patient populations were similar and the likelihood that this observation could have been made by chance is almost negligible. The mechanisms of action of IFN-α are very pleiotropic, and many mechanisms can be responsible for the observed anti-tumour effect. There are actions directly on the tumour such as an antiproliferative effect, and there are indications that the induction of the thymidase is related with this potential (Grander et al., 1990). On the other hand, immunological properties such as the expression of antigens on the tumour might play a role. The mechanism of action as elucidated in hairy cell leukaemia (Vedantham et al., 1992), the carcinoid (Grander et al., 1990) and the observation that the addition of 20 mg of prednisone had no impact on the anti-tumour effect (Fossa et al., 1990) suggest a direct effect on the tumour cell. Interferon-gamma is considered a true immunomodulating agent, predominantly on macrophages, with few direct anti-proliferative effects on tumour cells. The results with IFN-γ

Table III Characteristics of responding patients

| Age | Sex | PS | Site       | Size     | Response | Comment                     | Response duration (weeks) |
|-----|-----|----|------------|----------|----------|-----------------------------|--------------------------|
| 1   | 61  | M  | Lung       | 22 x 19  | PR       | PD in lungs and nodes, brain metastases. Dead due to malignant disease | 102                      |
| 2   | 41  | M  | Local      | 23 x 22  | CR       |                              | 68                       |
| 3   | 49  | M  | Nodes      | 30 x 35  | CR       | PD lungs, brain metastases. Dead due to malignant disease        | 45                       |
| 4   | 46  | M  | Nodes      | 30 x 25  | pCR      | No vital tumour at surgery                                      | 192 +                    |
| 5   | 53  | F  | Lung       | 15 x 10  | CR       |                              | 21                       |
| 6   | 55  | M  | Lung       | 20 x 11  | PR       | PD lungs. After metastasectomy NED. Brain metastases. After RT alive | 91                       |
| 7   | 66  | F  | Lung       | 49 x 23  | PR       | PD brain metastases. Death due to malignant disease              | 52                       |
| 8   | 65  | M  | Lung       | 23 x 20  | PR       | PD initial sites. Dead due to malignant disease                  | 43                       |
| 9   | 66  | F  | Nodes      | 25 x 40  | CR       | After surgery only fibrosis and non-vital tumour was seen (necrosis) | 211 +                    |

CDF, continuously disease free; NED, no evidence of disease; RT, radiotherapy.

Table IV Toxicity (WHO grade)

|                  | rIFN-α   | rIFN-α + IFN-γ |
|------------------|----------|---------------|
|                  | II (I)   | III (II)      |
|                  | II (I)   | III (II)      |
| Platelets        | 1        | 1             |
| Platelets        | 1        | 1             |
| WBC              | 7        | 0             |
| Pulmonary        | 4        | 2             |
| Fever            | 27       | 0             |
| Cutaneous        | 2        | 0             |
| Alopecia         | 1        | 0             |
| Cardiacs (rhythm)| 4        | 1             |
| Mucous           | 1        | 0             |
| Nausea and vomiting | 11      | 5             |
| Neurotoxicity    | 0        | 0             |
| Non-WHO          | 2-3      | 2-3           |
| Flu-like syndrome| 16       | 16            |
| Anorexia         | 21       | 21            |
| Mood alterations  | 8        | 6             |
| Fatigue          | 27       | 24            |
| Headache         | 5        | 8             |

II, moderate; III, severe.

obtained from pooled data is about 17% (Krown, 1987; Muss, 1988; Horoszewicz et al., 1989; De Mulder et al., 1991). Prognostic factors such as performance status, tumour volume, presence of bone metastases and disease-free interval are well recognised and are the main explanation for the variation in response observed in the various studies. There is no indication that the route of administration, schedule or the type of IFN-α is critical for the observed clinical results. Dose dependency is suggested but an adequate randomised study to address this question has never been performed. Very low daily dosages, i.e. below 10 x 10^6 IU daily, are probably ineffective. Our own observation in a small group of patients corroborates this experience (Geboers et al., 1988).

In the present multicentre study the activity of IFN-α is confirmed with an overall response rate of 13%. When only patients without their primary tumour are analysed, the response rate is 17%, which is consistent with the range observed in the literature. One should realise that these results were obtained with a relatively low dose of IFN-α (10 x 10^6 IU m^-2) and a twice-weekly schedule, again an indication that the regimen is not critical and that IFN-α given above a certain threshold is able to induce responses in sensitive tumours. A remarkable finding was that in two patients an objective response in the liver was seen.

The main purpose of the study was to study the relevance of the addition of IFN-γ, which was based both on laboratory observations as well as on the results of earlier studies. The results were very disappointing because only in two patients (4%) was an objective response observed and the study, initially planned as a randomised phase III study, was stopped after an interim analysis. As indicated before, the probability of obtaining these results if a difference of 10% in favour of the combination was actually present is extremely low. Equivalence in outcome or even the inverse outcome, i.e. a potential adverse effect of the combination, cannot be excluded with adequate power in view of the numbers involved, but this was not the purpose of the study. There is no satisfactory explanation for this result. Patient characteristics of the two patient populations were similar and the likelihood that this observation could have been made by chance is almost negligible. The mechanisms of action of IFN-α are very pleiotropic, and many mechanisms can be responsible for the observed anti-tumour effect. There are actions directly on the tumour such as an antiproliferative effect, and there are indications that the induction of the thymidase is related with this potential (Grander et al., 1990). On the other hand, immunological properties such as the induction of natural killer activity and the enhancement of the expression of antigens on the tumour might play a role. The mechanism of action as elucidated in hairy cell leukaemia (Vedantham et al., 1992), the carcinoid (Grander et al., 1990) and the observation that the addition of 20 mg of prednisone had no impact on the anti-tumour effect (Fossa et al., 1990) suggest a direct effect on the tumour cell. Interferon-gamma is considered a true immunomodulating agent, predominantly on macrophages, with few direct anti-proliferative effects on tumour cells. The results with IFN-γ
monotherapy are generally disappointing. The 30% response rate observed by Aulitzky et al. (1989), so far unconfirmed, applying an individually tailored dose of IFN-γ based on parameters of immune stimulation such as neopterin excretion, indicates the sensitivity of this disease depending on very specific requirements. The IFN-γ dose used in the present study was within the same range. One of the explanations of the generally low response rate in combination studies could be the relatively low dose of IFN-α given in these studies (De Mulder et al., 1991). In the present study this explanation is unlikely in view of the almost identical dose intensity of IFN-α in the two treatment arms.

Based on these results, the combination of IFN-α and IFN-γ in the dose and schedule described in this study cannot be recommended. Our results confirm the limited activity of IFN-α monotherapy in this disease.

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