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-α), 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-α2b (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 of rIFN-γ to rIFN-α2b treatment. Treatment consisted of rIFN-α2b 30 μg m⁻² = 10 x 10⁶ IU m⁻² s.c. twice weekly in arm A and the same dose of rIFN-α 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-α2b monotherapy arm and in 2/49 (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-α2b for the two treatment arms was the same. The addition of rIFN-γ does not improve the response rate of rIFN-α2b 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 (Ritchie et al., 1983). 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 17.6%; 2% CR and 15% PR). Experience with rIFN-γ in renal cell carcinoma is limited and, with a few exceptions, disappointing (Rinehart 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 (Czarnecki 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-α2b (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 U 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-α2b 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
(active 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-a2c and rIFN-γ (Genentech) were supplied by Boeh­
ringer Ingelheim (Alkmaar, The Netherlands) and provided
as a sterile lyophilised powder. The powder contained 15 µg
of IFN-a2c with a degree of purity of >98% and a specific
activity of 4 × 10^6 IU/15 µg^1 based on the NIH IFN-α
standard G0-23-901-527 for rIFN-α or 150 µg of IFN-γ with
a specific activity of 2 × 10^8 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
ately before use to yield rIFN-a2c and rIFN-γ concentrations
of 5 × 10^6 IU ml^-1 and 10 × 10^6 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-a2c monotherapy and arm B con­
sisted of the same dose of rIFN-a2c plus rIFN-γ. rIFN-γ was
given subcutaneously according to the WHO grading system.

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,
bilirubin, and gamma-glutamyl transferase. Total protein and
subfractions, cholesterol, triglycerides and interferon
antibodies were monitored every 4 weeks. Electrocardio­
graphy was repeated when indicated. Tumours were
measured every 4 weeks with standard radiographic, com­
puterised tomographic or ultrasonographic techniques as
appropriate.

Evaluation criteria
The criteria for measurability of disease were according to
the EORTC Data Center procedures manual (van Oosterom
et al., 1993). Nodes smaller than 2 cm and liver metastases
smaller than 3 cm in diameter were not considered to be
measurable or evaluable. Complete remission (CR) was
defined as the disappearance of all clinical evidence of
tumour for a minimum of 4 weeks. Partial remission (PR)
was defined as a 50% or greater decrease in the sum of the
products of the perpendicular diameters of all measurable
lesions, without simultaneous increase in the size of any
existing lesion or development of new lesions, for a minimum
of 4 weeks. Progressive disease (PD) was defined as a 25%
or greater increase in the size of at least one existing lesion
or the appearance of new lesions. SD was defined as a
decrease of less than 50% or an increase of less than 25%.
For CR and PR duration of response was measured from the day
of the start of treatment until disease progression or death.
A patient was evaluable for toxicity when at least 4 weeks'
treatment was given. A patient was evaluable for response
when at least 8 weeks treatment was completed. However, all
patients with PD, irrespective of the duration of treatment,
were included in the response analysis. In case of stable
disease treatment was to be discontinued after 6 months.
When a PR or CR was seen treatment was to be continued
to 1 year from the date of CR/PR.

Statistical methods
The expected response rate for the combination arm was
25–30%; the expected response rate for the monotherapy
arm was between 15% and 20%. The minimal difference in
response rate which was of practical interest was defined to
be 15%. To detect such a difference at error rates α = 0.05
and β = 0.20, 94 eligible and evaluable patients were required
on each treatment. In order to ensure that continuation of
the trial was ethical, an interum analysis was planned after
receipt of the data for the first 40 patients in each arm. The
response rates were compared using a two-sided Fisher exact
test. The duration of response and the duration of survival
were estimated by the Kaplan–Meier technique and com­
pared using a two-sided log-rank test.

Results
Between November 1988 and September 1990, 102 patients
entered the study and were randomly assigned to treatment as
follows: arm A, 54 patients; arm B, 48 patients. Four
patients were ineligible, one on treatment A and three on
Treatments B: one patient had a second primary, one patient
did not have evaluable lesions and two patients started within
4 weeks after tumour nephrectomy without documented pro­
gression of metastatic disease. Nine eligible patients were
not evaluable for response.

Patient characteristics at entry are depicted in Table I and
are well balanced in the two treatment groups. For the entire
group, 68% were male and 43% had a WHO performance
status of 0. Eighteen per cent of the patients started treat­
ment with the primary tumour in situ. Prior radiotherapy,
mainly on threatening bone lesions, was given in 10% of the
patients. Lung metastases were present in almost all patients.
In 27% lung was the only site of disease. Liver metastases
alone or in combination with other sites were seen in 14%.
The majority of the patients had only one or two sites of
disease (76%).
### Treatment efficacy

Considering all eligible patients (98) entered into the trial, the response rates were as follows: rIFN-α, monotherapy, one CR, one pathological CR, five PRs and 19 no change (NC), overall 13%; rIFN-α + rIFN-γ, one pathological 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 pathological 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.

### Discussion

There is no doubt that interferons can induce responses in advanced renal cell carcinoma. The response percentage...
The results with IFN-\(\gamma\) are well recognised and are the main explanation for the variation in response observed in the various studies. There is an indication that the induction of natural killer activity and the enhancement of cytotoxicity is related with this potential (Grander et al., 1990). The mechanism of action as elucidated in hairy cell leukaemia (Vedantham et al., 1990) suggests a direct effect on the tumour cell.

On the other hand, immunological properties such as the proliferative effects on tumour cells. The results with IFN-\(\gamma\) and IFN-\(\alpha\) in RCC (PHM De Mulder et al., 1990) suggest a direct effect on the tumour cell.

When only patients with 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-\(\alpha\) \((10 \times 10^{6} \text{ IU m}^{-2})\) and a twice-weekly schedule, again an indication that the regimen is not critical and that IFN-\(\alpha\) 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-\(\alpha\), 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-\(\alpha\) 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 2',5'-oligoadenylate synthetase 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 antiproliferative effects on tumour cells. The results with IFN-\(\gamma\)

### Table III  Characteristics of responding patients

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>PS</th>
<th>Site</th>
<th>Size</th>
<th>Response</th>
<th>Comment</th>
<th>Response duration (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61</td>
<td>M</td>
<td>Lung</td>
<td>22 x 19</td>
<td>PR</td>
<td>PD in lungs and nodes, brain metastases.</td>
<td>102</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dead due to malignant disease</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>41</td>
<td>M</td>
<td>Lung</td>
<td>10 x 10</td>
<td>CR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>49</td>
<td>M</td>
<td>Nodes</td>
<td>30 x 35</td>
<td>PR</td>
<td>PD lungs, brain metastases.</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dead due to malignant disease</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>46</td>
<td>M</td>
<td>Nodes</td>
<td>30 x 25</td>
<td>pCR</td>
<td>No vital tumour at surgery</td>
<td>192 +</td>
</tr>
<tr>
<td>5</td>
<td>53</td>
<td>F</td>
<td>Lung</td>
<td>15 x 10</td>
<td>PR</td>
<td>PD initial sites. Dead due to malignant</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15 x 15</td>
<td></td>
<td>disease</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>55</td>
<td>M</td>
<td>Lung</td>
<td>20 x 11</td>
<td>CR</td>
<td>PD lungs. After metastasectomy NED.</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>13 x 16</td>
<td></td>
<td>Brain metastases. After RT alive</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>66</td>
<td>F</td>
<td>Lung</td>
<td>49 x 23</td>
<td>PR</td>
<td>PD brain metastases. Death due to malignant</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 x 6</td>
<td></td>
<td>disease</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>65</td>
<td>M</td>
<td>Lung</td>
<td>23 x 20</td>
<td>PR</td>
<td>PD initial sites. Dead due to malignant</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15 x 13</td>
<td></td>
<td>disease</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>66</td>
<td>F</td>
<td>Nodes</td>
<td>25 x 40</td>
<td>CR</td>
<td>After surgery only fibrosis and non-vital</td>
<td>211 +</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>tumour was seen (necrosis)</td>
<td></td>
</tr>
</tbody>
</table>

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

### Table IV  Toxicity (WHO grade)

<table>
<thead>
<tr>
<th></th>
<th>rIFN-(\alpha)</th>
<th>rIFN-(\alpha) + IFN-(\gamma)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>Platelets</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>WBC</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Fever</td>
<td>27</td>
<td>9</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Aleopnea</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cardiac (rhythm)</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Mucous</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Non-WHO</td>
<td>2-3</td>
<td>2-3</td>
</tr>
<tr>
<td>Flu-like syndrome</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Anorexia</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td>Mood alterations</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Fatigue</td>
<td>27</td>
<td>24</td>
</tr>
<tr>
<td>Headache</td>
<td>5</td>
<td>8</td>
</tr>
</tbody>
</table>

II, moderate, III, severe.
References


The 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. 

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 therapy, 1983-1988, and the emerging role of monoclonal antibodies for renal cancer. Urol. Int., 44, 338-345.