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# RECOMBINANT LEUKOCYTE INTERFERON ALPHA-2A AND MEDROXYPROGESTERONE IN ADVANCED RENAL CELL CARCINOMA

## A randomized trial

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**Abstract**

In a randomized study of advanced renal cell carcinoma 60 patients were allocated to treatment with either recombinant interferon alpha-2a or medroxyprogesterone acetate. Correlation between the dose of interferon alpha-2a and plasma-concentration indicated linear kinetics. Survival was similar in the two treatment groups. Only one complete and one partial response were seen in the interferon group and only one complete response in the medroxyprogesterone group, indicating a low therapeutic potential of both interferon and medroxyprogesterone. Interferon influenced the serum liver enzyme levels; increased transaminases were seen in 17 patients treated with interferon but in only four patients in the medroxyprogesterone group. Two patients had very high serum liver-enzyme levels concomitant with intolerable tiredness, in both patients the symptoms disappeared and the enzymes normalized after discontinuation of the interferon treatment. Antibodies to interferon developed frequently in patients receiving high dose oligomeric interferon therapy but rarely in patients receiving low dose monomeric interferon treatment.

*Key words:* Renal adenocarcinoma, advanced, medroxyprogesterone, interferon, adverse effects, anbibodies, liver enzymes, random allocation.

There is a need for treatment regimens in advanced renal cell carcinoma. In an earlier study at our institute, partially purified human leukocyte alpha interferons were administered to 11 patients with pulmonary metastasis of this disease (1) and three patients responded. After that, a larger trial was performed concerning the efficacy and tolerability of interferon as compared to medroxyprogesterone which is often used for this patient category at our hospital. Recombinant interferon seemed to offer an alternative to human leukocyte interferons and was used in the study. The results obtained are the subject of the present report.

### Material and Methods

Between January 27, 1983, and September 9, 1985, 60 patients with metastatic renal cell adenocarcinoma were randomly allocated to receive either interferon or medroxyprogesterone. The study was approved of by the Ethical Committee of the Karolinska Hospital and by the Swedish National Board of Health and Welfare. After appropriate information, each patient gave an oral consent to be included in the trial.

*Treatments.* Recombinant leukocyte interferon alpha-2a (Roferon-A, below for brevity called interferon) was used and the first 10 patients received an initial dose of 50 MU/m$^2$ 3 times a week i.m. Due to extensive side effects, mainly tiredness/lethargy, the first protocol was amended and the initial dose was lowered to 10 MU/m$^2$ 3 times a week. It was decided that the dose should be

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escalated weekly by 2.5 MU/m$^2$ to a maximum of 20 MU/m$^2$ whenever possible. The dose was reduced, or the treatment temporary discontinued, when the side effects were too troublesome. Almost all subjects ingested 1 g of paracetamol before and sometimes also after the interferon injection in an attempt to diminish the acute side effects such as fever and chills.

Oligomeric interferon preparations contain several molecules of interferon alpha-2a linked together while monomeric interferon consists of single molecules. The first 18 patients in the study were given oligomeric interferon, thereafter monomeric interferon was administered.

The patients in the comparison group received 1 g medroxyprogesterone acetate (Farlutal) i.m. 3 times weekly for 5 weeks and therafter 1 g once a week.

Both treatments continued until the patient suffered from intolerable side effects or rapidly progressing disease. The progression date, as defined below for enrollment in the analysis of the overall outcome, was determined retrospectively and therefore did not influence the discontinuation of treatment. Data on adverse events are given for the whole treatment period. Survival is the time period from the start of treatment until death or until study closure at February 1, 1986, whichever was appropriate.

*Patients.* Patients with a locally recurrent or metastatic adenocarcinoma of the kidney, aged between 18 years and 'a physiological age of 70', and with a life expectancy of more than 12 weeks, were accepted for the study. The disease had to be histologically and/or cytologically diagnosed.

The initial protocol required a nephrectomy of the primary tumor but after the amendment (mentioned above) this was not necessary. Previous irradiation of the disease or excision of metastases was accepted but not any concomitant medical treatment of the renal cell carcinoma. Subjects with a severe intercurrent disease or any impaired function as judged by blood examinations (creatinine >200 mmol/l, total bilirubin >30 mmol/l, white blood cell count $<3\times10^9$/l, granulocytes $<1\times10^9$/l, platelets $<100\times10^9$/l, or serum calcium >3 mmol/l) were not included in the study. Concomitant medication with corticosteroids was not allowed and concurrent medication with anti-inflammatory drugs, such as acetylsalicylic acid, was not advisable.

Among the 60 patients who entered the trial 15 were crossed over to interferon treatment after termination of medication with medroxyprogesterone. No data is given in this report for the interferon treatment after crossover, except for two patients with side effects. Some patients violating the protocol are mentioned in Results.

Physical examination was performed at the initiation of treatment and every 4 weeks thereafter. Urine analyses and estimation of interferon antibodies were carried out at the beginning of treatment and at 4-weekly intervals. Blood chemistry was required every 2 weeks.

At the outset all palpable tumors were measured. In addition, abdominal computerized tomography, bone radionuclide scan and chest radiogram were performed. During treatment, all special examinations with abnormal results at the outset were followed every 4 weeks. At six months, or at the termination of treatment, whichever came first, abdominal computerized tomography, bone radionuclide scan and chest radiogram were repeated and palpable tumors measured. All radiograms and scans were examined by one radiologist (VS) who did not know what treatment had been given. As a rule 1–3 indicator lesions were selected for each tumor site and the lesions were then measured for all examination dates available.

The WHO criteria (2) were applied in defining the outcome. For each lesion, the individual remission was determined. If the approximated area of the lesion increased by more than 25%, the lesion was judged to be progressing. A decrease by more than 50% was classified as a partial remission, and complete disappearance as complete remission. A lesion not fulfilling these criteria was assigned as no change.

The overall outcome for a subject was assessed in two steps. First, a progression date was defined as the date when a new lesion appeared, or when one of the lesions showed progression. Next, the best overall result between outset and the progression date for the subjects was chosen. Complete remission required disappearance of all known lesions for at least one month. Partial remission required that the area sum of all indicator lesions was half of the sum at the outset. When the criteria for a complete or partial remission were not fulfilled, and at least one further examination of all indicator lesions as compared to the outset did not show any progressing lesion the overall outcome was considered as stable disease. If no special examinations were performed after the initiation of treatment, the patient's disease was classified as non-assessable.

The physical examination included registration of blood pressure. Assessment of performance status was made according to Karnofsky et al. (3). During treatment, an attempt was made to register all reported adverse symptoms that the patients did not have at the outset. Fever and chills for some hours after the injection of drug as well as pain in the joints and muscles were all included as 'flu-like symptoms'. Weight loss was registered as an adverse event when the weight decreased by more than 5% compared to the value at outset. Transaminases (glutamic oxaloacetic transaminase/aspartase amino transferase = GOT/ASAT and glutamic pyruvic transaminase/alanine amino transferase = GPT/ALAT), alkaline phosphatase, bilirubin and serum-creatinine contributed adverse events when increased by 25% as compared to the upper 'normal limit' given by the laboratory. The adverse event was graded as moderate when the value was 2.6–5 times the upper limit, as severe when it was for 5.1–10 times the upper limit and intolerable when it was more

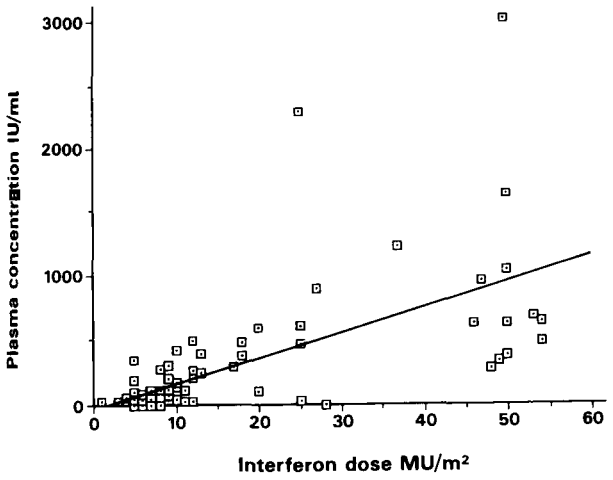


Fig. 1. Correlation between dose of interferon alpha-2a and the plasma concentration. A square represents for each dose the plasma concentration for one patient. When several measurements of the concentration are available for one patient on a given dose, the mean plasma concentration between the different measurements was used (r=0.79).

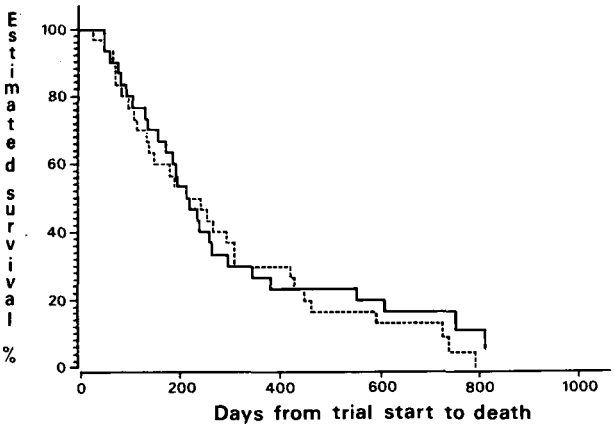


Fig. 2. Survival for patients treated with either interferon alpha-2a (---) or medroxyprogesterone (——).

than 10 times the upper limit. Only a moderate or high increase of serum alkaline phosphatases was notified as an adverse event. Registration of anemia required a blood count of less than 110 g/l and leukopenia a white blood cell count less than $4.0\times10^9$/l. A thrombocyte count below $100\times10^9$/l was registered as thrombocytopenia. Total calcium values above 3.0 mmol/l were defined as adverse events of hypercalcemia. The grading for gastrointestinal adverse events was arbitrary while protein- and hematuria required the presence of protein or blood in the urine as determined by a uristick.

The concentration of interferon in plasma was determined as described by Gallaty (4). Interferon antibodies were detected by an anti-viral assay (5, 6), believed to identify *in vitro* neutralizing antibodies, and with an enzyme immunosorbent assay (6).

An overall estimate of the patient's tolerance to the medication was carried out by the investigator six months after the outset of treatment using the following categories: Very good = no adverse events judged as possibly related to the test medication; Good = no dose reduction required because of adverse events; Fair = dose reduction required because of adverse events judged to be possibly related to test medication; Poor = treatment temporarily discontinued because of adverse events; Bad = treatment permanently discontinued because of adverse events.

The patients were treated by different physicians. Three of the authors (GS, BC and EB) transferred data into the patient record forms. The information so obtained was computerized and analysed by Hoffmann-La Roche in Basle, Switzerland.

*Statistical analysis.* Assuming a binominal distribution, 95% confidence limits were determined for some proportions. In comparing proportions between treatment groups Fisher's exact test was applied and 2-sided p-values are reported.

## Results

*Patient characteristics.* The median age (with range) for the 30 patients allocated to interferon was 63 (39–73) years and for the 30 patients allocated to medroxyprogesterone 62 (40–77) years. The interferon group included 9 females and the medroxyprogesterone group 6 females. The median body surface was 1.9 $m^2$ in both treatment groups. In the interferon group, the disease first appeared with metastates for 13 patients, while the corresponding figure for the medroxyprogesterone group was 16. In the interferon group, the primary kidney tumor in one patient was well differentiated, in 10 moderately differentiated and in 11 poorly differentiated adenocarcinoma while for 8 patients information on the degree of differentiation was not available. The corresponding figures for the medroxyprogesterone group was well differentiated adenocarcinomas in 2 patients, moderately differentiated in 17, poorly differentiated in 8 and information not available for three.

Three patients in each group had not had the primary tumor excised prior to the outset of the trial. The primary tumor in the kidney was surgically embolized for one patient in the medroxyprogesterone group, otherwise the prior therapy of the renal cell carcinoma was similar for the two groups. In the interferon group, 14 patients had bone metastases compared to 11 patients in the medroxyprogresterone group.

The interval between primary diagnosis and the outset of the test medication (with range) in the study was 267 days (16–5459) for the interferon group and 209 days (28–4796) for the medroxyprogesterone group. The initial

**Table 1**

*Outcome. Number of subjects (No.) proportion of subjects (%) with 95% confidence interval (95% CI) in each outcome category*

| Remission | Interferon group | | | Medroxyprogesterone group | | |
|---|---|---|---|---|---|---|
| | No. | Prop. % | 95% CI | No. | Prop. % | 95% CI |
| Complete remission | 1 | 3 | 0–17 | 1 | 3 | 0–17 |
| Partial remission | 1 | 3 | 0–17 | 0 | 0 | 0–12 |
| No change | 4 | 13 | 4–31 | 3 | 10 | 2–27 |
| Progressive disease | 19 | 63 | 44–80 | 22 | 73 | 54–88 |
| Not assessable with special examinations | 5 | 17 | 6–35 | 4 | 13 | 8–31 |

performance status was somewhat lower in the interferon group, with a median Karnofsky index of 85 versus 90 in the medroxyprogesterone group. Fifteen patients in the interferon group versus 14 patients in the medroxyprogesterone group had a Karnofsky index of 80 or less.

*Concentration of interferon.* The plasma-concentration of interferon (Fig. 1) was dependent on the dose given. Three patients had plasma-concentration levels above 2000 IU/ml. All three patients developed antibodies to interferon, one of them had a complete remission and the other two remissions of their lung lesions.

*Efficacy.* Survival (Fig. 2) was similar for the two treatment groups. Only three patients had an overall remission during treatment (Table 1).

One patient in the interferon group had two lung lesions, seen in several consecutive radiograms, and an enlarged lymph node. He had a complete remission 84 days after the start of treatment. This lasted for 126 days. His lowest leukocyte count was 5.7. One month prior to the complete remission the serum interferon level was 2655 IU per ml as determined by an anti-viral assay. Only two other patients had such a high level of serum interferon. One month after the date of the remission anti-interferon antibodies were detected by the immunosorbent assay. This assay had unfortunately not been performed previously. Two months later a weak reaction of 200 IU per ml was detected by the anti-viral assay.

One patient in the interferon group had a partial remission of two lesions in the lung on day 84. The remission lasted for 176 days. This patient in addition had a destruction in vertebra XII. The lesion was irradiated and disappeared completely but was not included in the overall evaluation of the outcome.

One patient in the medroxyprogesterone group had two lung lesions, documented by one radiogram only. These lesions disappeared on day 36 and the patient was still in a complete remission by day 626.

For a more strict evaluation of the efficacy nine patients had to be excluded. However, this exclusion did not essentially change the survival curves or the proportion of responding patients in the two compared groups. Two patients were excluded since they were accepted for the study although violating the initial protocol requiring a prior nephrectomy. Two patients were excluded since they were older than 75 years of age; the inclusion criteria required a 'physiologic age' of 70 years or less. One patient had two primary malignancies and four patients were not assessable. In addition, one patient started prednisone treatment on day 21 and was only regarded as evaluable up to that time.

*Tolerability.* The tolerability in the interferon group was assessed as 'good and very good' in 8 patients, 'fair' in 13 patients, 'poor' in 3 patients and 'bad' in 6 patients. All patients but one in the medroxyprogesterone group had a very good or good tolerability.

*Liver enzymes.* Increased levels of serum transaminases was seen in a higher proportion of the patients treated with interferon ($p<0.001$) than those treated with medroxyprogesterone (Table 2). Two patients had very high levels (Table 3). Both were without signs of liver tumors and had, as described below, in addition intolerable tiredness.

One patient was a 59-year-old man with lung lesions detected during the study. A radionuclide scan of the liver performed on day 87 was judged to be normal. All the tested serum liver enzymes were within the normal range at outset of interferon therapy. Both types of transaminases increased in parallel. On day 8, the increase was minimal, on day 29 it was moderate, by day 57 it bordered on severe and the peak values of 1025 U/l for GPT/ALAT and 944 U/l for GOT/ASAT were seen on day 87. That day the patient had, in addition, an intolerable tiredness and intolerable nausea/vomiting and the treatment was therefore discontinued. Furthermore, on the same day serum alkaline phosphatase levels reached a peak of 762 U/l and glutamyl transpeptidase a peak of 504 U/l. However, serum bilirubin levels increased more slowly and its peak of 87 mmol/l was reached 5 weeks later. All these serum enzyme levels decreased rapidly and the symptoms disappeared after discontinuation of interferon treatment.

In another patient, a 66-year-old woman, with lung lesions, a radionuclide scan of the liver on day 102 and an

**Table 2**

*Adverse events during treatment. Number (No.) and proportion of subjects with 95% confidence interval (95% CI) experiencing at least one adverse during treatment*

| Event | Interferon group | | | Medroxyprogesterone group | | |
|---|---|---|---|---|---|---|
| | No. | Prop % | 95% CI | No. | Prop. % | 95% CI |
| General | | | | | | |
| Flu-like symptoms | 30 | 100 | 88–100 | 1 | 3 | 0–17 |
| Tiredness | 20 | 67 | 47–83 | 3 | 10 | 2–27 |
| Weight loss | 7 | 23 | 10–42 | 5 | 17 | 6–35 |
| Liver and biliary | | | | | | |
| Increased serum transaminases | 17 | 57 | 37–75 | 4 | 13 | 4–31 |
| Increased serum alkaline phosphatases | 5 | 17 | 6–35 | 1 | 3 | 0–17 |
| Increased serum bilirubin | 1 | 3 | 0–17 | 0 | 0 | 0–12 |
| Hematology | | | | | | |
| Anemia | 12 | 40 | 23–59 | 9 | 30 | 15–49 |
| Leukopenia | 14 | 47 | 26–66 | 0 | 0 | 0–12 |
| Thrombocytopenia | 2 | 7 | 1–22 | 0 | 0 | 0–12 |
| Gastrointestinal | | | | | | |
| Appetite loss | 6 | 20 | 8–39 | 1 | 3 | 0–17 |
| Diarrhoea | 1 | 3 | 0–17 | 0 | 0 | 0–12 |
| Nausea/vomiting | 10 | 33 | 17–53 | 3 | 10 | 2–27 |
| Urinary disorders | | | | | | |
| Proteinuria | 6 | 20 | 8–39 | 1 | 3 | 0–17 |
| Hematuria | 3 | 10 | 2–27 | 0 | 0 | 0–12 |
| Respiratory | | | | | | |
| Cyanosis | 1 | 3 | 0–17 | 0 | 0 | 0–12 |
| Dyspnoea | 2 | 7 | 1–22 | 1 | 3 | 0–17 |
| Cardiovascular | | | | | | |
| Cardiac infarction | 1 | 3 | 0–17 | 0 | 0 | 0–12 |
| Thrombosis | 1 | 3 | 0–17 | 0 | 0 | 0–12 |
| Hypertension | 0 | 0 | 0–12 | 2 | 7 | 1–22 |
| Skin | | | | | | |
| Alopecia | 1 | 3 | 0–17 | 0 | 0 | 0–12 |
| Itching | 3 | 10 | 2–27 | 1 | 3 | 0–17 |
| Perspiration | 0 | 0 | 0–12 | 1 | 3 | 0–17 |
| Miscellaneous | | | | | | |
| Creatinine increase | 0 | 0 | 0–12 | 7 | 23 | 10–42 |
| Hypercalcemia | 0 | 0 | 0–12 | 4 | 13 | 4–31 |
| Nose bleeding | 1 | 3 | 0–17 | 0 | 0 | 0–12 |
| Petechial bleedings | 1 | 3 | 0–17 | 0 | 0 | 0–12 |
| Severe anxiety | 2 | 7 | 1–22 | 0 | 0 | 0–12 |
| Vertigo | 1 | 3 | 0–17 | 1 | 3 | 0–17 |
| Tinnitus | 1 | 3 | 0–17 | 0 | 0 | 0–12 |
| Cramps, unspecified | 1 | 3 | 0–17 | 0 | 0 | 0–12 |
| Diplopia | 1 | 3 | 0–17 | 0 | 0 | 0–12 |
| Pain behind eye | 1 | 3 | 0–17 | 0 | 0 | 0–12 |
| Confusion | 0 | 0 | 0–12 | 1 | 3 | 0–17 |
| Tremor | 0 | 0 | 0–12 | 1 | 3 | 0–17 |

ultrasound investigation of the liver on day 205 were judged to be normal. Serology for hepatitis was negative. Slight pain during palpation below the right arcus was reported on day 205. All serum liver enzymes were within the normal range at the outset of interferon therapy. Again, the transaminases increased in parallel and in this patient the peak values of 465 U/l for GPT/ALAT and 482 U/l for GOT/ASAT were seen on day 202. On the same day peak values of 714 U/l for alkaline phosphatase and 69 U/l for serum bilirubin were registered. Serum glutamyl transpeptidases had a peak 14 days later with 1584 U/l. This patient had intolerable tiredness and nausea/vomiting as well. After the discontinuation of interferon treatment all serum enzyme levels normalized and the above mentioned symptoms disappeared.

*Hematology*. Slightly more patients treated with inter-

feron suffered from anemia than those treated with medroxyprogesterone. Leukopenia was only seen in the interferon group and 4 patients had a nadir count of less than $2.0\times10^9$/l.

One patient, a 66-year-old man, was allocated to medroxyprogesterone treatment 595 days after the nephrectomy. On day 37 he was crossed over to receive interferon therapy. Initially during this treatment he had a slight anemia and a moderate leukopenia. On day 151 the disease was assessed as rapidly progressing and at day 176 the treatment with interferon was stopped. At that date, the hemoglobin value was 59 g/l, the white blood cell count $2.1\times10^9$/l and the platelet count $43\times10^9$/l. The patient had petechial bleedings that were probably related to the thrombocytopenia and consequently to the interferon treatment. In addition, he was very tired and complained of nausea and vomiting. After the discontinuation of the treatment the patient received terminal care at his home. No additional examinations were made to further clarify the cause of the pancytopenia.

*Flu-like symptoms and tiredness.* Flu-like symptoms in connection with the injections were seen in all patients treated with interferon (Table 2). All patients experienced relief, and sometimes complete disappearance, of symptoms when the treatment had continued for some weeks.

More patients treated with interferon ($p<0.001$) than with medroxyprogesterone experienced tiredness (Table 2). For 9 of these the tiredness was judged to be intolerable (Table 3). For almost all patients the tiredness diminished after dose reduction.

*Other adverse events.* A 3-fold increase of nausea and/or vomiting (Table 2) was seen in the interferon group as compared to medroxyprogesterone ($p=0.057$). A 6-fold increase ($p=0.103$) was seen for appetite loss. All three patients with intolerable vomiting had increased levels of serum transaminases. Two of these patients are described above. The third patient had increased levels of serum transaminases at outset. Proteinuria and hematuria occurred somewhat more frequently in the patients treated with interferon.

One 71-year-old man had a cardiac infarction on day 41 of interferon treatment. Before outset, he was prescribed diuretics due to hypertension and a heart volume with an upper borderline value (970 $cm^3$). Unfortunately, no ECG was performed at outset of interferon treatment. After the infarction he had continuous sequelae of angina pectoris and atrial fibrillation.

Another patient, a 69-year-old man, experienced severe anxiety immediately after the first interferon injection. This was resolved the same day with benzodiazepin medication. On day 10 the same patient developed a deep venous thrombosis and the interferon therapy was discontinued.

One further patient, a 66-year-old woman, developed severe anxiety. It occurred on day 3 and after three further injections she experienced such an anxiety, dyspnea and retrosternal breast pain that she was moved to the emergency unit. However, all tests performed were negative, she recovered and no more anxiety periods were reported during 169 days of treatment.

One patient developed hypotonic muscular tension on day 814 after crossover to interferon. These symptoms disappeared after discontinuation of interferon treatment. No EMG or other tests were performed during the episode.

**Table 3**

*Adverse events. Number of subjects in different categories of severity for certain adverse events. The total number of subjects in each group is 30. To the right p-value when comparing the proportion of subjects with any versus no adverse events between treated groups*

| | Interferon | Medroxyprogesterone | |
|---|---|---|---|
| Increased transaminases | | | |
| None | 13 | 26 | |
| Minimal (0.9–1.7 mkat/l) | 9 | 3 | |
| Moderat (1.8–3.5 mkat/l) | 6 | 1 | |
| Severe (3.6–7.0 mkat/l) | 0 | 0 | |
| Intolerable (7.1–mkat/l) | 2 | 0 | |
| | | | $p<0.001$ |
| Anemia | | | |
| None | 18 | 21 | |
| Minimal (95–109 g/l) | 4 | 3 | |
| Moderate (80–94 g/l) | 6 | 4 | |
| Severe (65–79 g/l) | 2 | 1 | |
| Intolerable (<65 g/l) | 0 | 1 | |
| | | | $p=0.6$ |
| Leukopenia | | | |
| None | 16 | 30 | |
| Minimal ($3.0–3.9\times10^9$/l) | 6 | 0 | |
| Moderate ($2.0–2.9\times10^9$/l) | 4 | 0 | |
| Severe ($1.0–1.9\times10^9$/l) | 3 | 0 | |
| Intolerable ($<1.0\times10^9$/l) | 1 | 0 | |
| | | | $p<0.001$ |
| Tiredness | | | |
| None | 10 | 27 | |
| Minimal | 1 | 2 | |
| Moderate | 3 | 1 | |
| Severe | 7 | 0 | |
| Intolerable | 9 | 0 | |
| | | | $p<0.001$ |
| Nausea/vomiting | | | |
| None | 20 | 27 | |
| Nausea | 1 | 0 | |
| Transient vomiting | 5 | 3 | |
| Severe vomiting | 1 | 0 | |
| Intolerable, intractable nausea/vomiting | 3 | 0 | |
| | | | $p=0.057$ |
| Proteinuria | | | |
| None or minimal | 25 | 29 | |
| Moderate (2–3+) | 5 | 1 | |
| Severe (4+) | 0 | 0 | |
| Intolerable (nephrotic syndrome) | 0 | 0 | |
| | | | $p=0.109$ |

More adverse events of creatinine increase (p=0.011) were seen in the medroxyprogesterone group. Four patients treated with medroxyprogesterone had increased serum calcium levels and one patient had confusion and hallucination.

*Anti-interferon antibodies.* Antibodies against interferon were demonstrated in 5 patients by the enzyme immunosorbent assay and in 2 patients by the anti-viral assay. In the patients receiving a high initial dose, 4 out of 10 developed anti-interferon antibodies while only one out of 20 patients receiving a low dose had detectable antibodies. The proportion (with 95% confidence interval) of patients developing antibodies were 40% (12–74%) and 5% (0–25%) in the respective group (p=0.03). All 10 patients receiving a high initial dose of interferon were treated with oligomeric interferon. Moreover, all 5 patients with detectable antibodies were given oligomeric interferon.

One patient, as described above, had a documented complete remission at the time the interferon antibodies were detected. Another patient, also mentioned above, had a partial remission documented for lung lesions one month prior to the interferon antibodies were detected and a partial remission of a tumor in the kidney a few days after the antibodies were detected. He also had a stable disease in his liver. However, the first radiogram, taken three months after treatment start and some days after the detection of the interferon antibodies, showed a progressing lesion in the bone. Hence, the overall outcome was assessed as a progressive disease.

A third patient had a progressive lesion in the suprarenal gland 3 months after initiation of treatment. The lesion was, however, surgically removed and the interferon treatment continued. After another 4 months, antibodies were detected by the use of the anti-viral assay and after another 12 months the lung lesions, previously decreasing in size, disappeared completely.

One patient had stable lung lesions but a progressive lesion in the abdomen, defining a progressive disease. The only lesion detected for patient number 24 was a subcutaneous tumor that progressed.

## Discussion

The study indicates that very few patients with advanced renal cell carcinoma benefits from treatment with recombinant interferon alpha-2a as the only anti-tumoral regimen. Indeed, many of the patients presented serious adverse events but no improvement of their disease. The survival was almost identical in the two treatment groups.

*Plasma-concentration.* The plasma-concentration of the interferon was dependent on the dose given (Fig. 1), indicating linear kinetics of the interferon within the dose interval studied.

*Efficacy.* In a previous study at our hospital (1), 11 patients with pulmonary lesions were treated with human leukocyte alpha interferons. Of these, 3 responded, giving a proportion of responding subjects (with 95% confidence interval) of 27% (6–61%). However, the selection of patients were completely different in the two investigations. In the present study, almost all referred patients with metastatic renal cell carcinoma were accepted for the study, and most of these had a large tumor burden. In the previous study, only patients with persistent lung lesions were accepted and most patients had a relatively small tumor burden. So, the two studies cannot be enrolled for a comparison of the responding proportions of subjects treated with the two types of interferon. However, as for example pointed out by Porzsholt et al. (7), it is possible that human leukocyte alpha interferons are more efficient in treating renal cell carcinoma than recombinant interferon alpha-2a.

It also remains uncertain whether the low proportion of patients with a remission in this study, as compared to earlier phase-II studies (10, 11), can be explained by a difference in the proportion of included patients with a high tumor burden. Another explanation could be a more strict application of the WHO-criteria for a patient's overall outcome of a remission in our study as compared to the earlier reports.

It is noteworthy that all three patients with serum interferon levels above 2000 U/l had remission of tumors. The anti-tumoral activity against renal cell carcinoma of recombinant interferon-alpha may be dependent on the serum interferon level and thus, if the linear kinetics of drug as indicated in this study holds true, of the dose. The mechanism for the anti-tumoral activity against renal cell carcinoma remains unclear and, as discussed by for example Porzsholt et al. (7), may differ from the mechanism for the activity against hairy cell leukemia.

*Tolerability.* Two patients suffered from severe anxiety initially during interferon treatment. The link to the interferon was difficult to assess. The same conclusion holds for the patient with the cardiac infarction and the one with thrombosis.

The study leaves few doubts that interferon treatment can increase the levels of certain liver enzymes in the serum, previously described in patient series without a control group, e.g. reported by Quesada et al. (8), Umeda & Niijima (9) and Trump et al. (10). It is notable that the two patients who acquired very high levels of serum transaminases at the same time complained of intolerable tiredness as well as nausea and vomiting, and that both the symptoms and the increased enzyme levels disappeared after discontinuation of the treatment. There may be some connection between the liver toxicity and the tiredness and nausea.

Eisenhaver et al. (11) reports on a patient with renal cell carcinoma who received human lymphoblastoid interferon. On the day for the 18th dose the patient's pretreatment platelet cell count of $321 \times 10^9$/l fell to less than $10 \times 10^9$/l within 24 h. This was associated with the devel-

opment of a petechial rash and a buccal hematoma as well as high levels of platelet-associated IgG. The thrombocytopenia observed in the present study in two patients may depend on the treatment with interferon.

*Formation of antibodies.* A higher proportion of the patients receiving a high initial dose of interferon developed antibodies. The tendency to develop antibodies may hence depend on the plasma-concentration of interferon but all 5 patients developing antibodies were treated with oligomeric interferon. Hence, the dosage and type of interferon was highly correlated and the relation between dosage and antibody formation may to a large part be explained by confounding from the type of interferon, or vice versa.

*Epilogue.* Recombinant interferon alpha-2a is a drug with antitumoral activity against renal cell carcinoma (12) but also with serious side effects requiring careful handling. The drug is very useful in the treatment of some other disease, e.g. hairy-cell leukemia (13, 14). Although it was impossible in this study to collect the information on adverse effects without the investigator knowing what treatment had been given, our impression is that the sensitivity and specificity in the registration is similar between the treatment groups. This also holds true for the laboratory tests. Hence, the present documentation of the side effects of interferon may prove valuable. For example, we saw an impressive correlation between treatment with interferon and increased serum liver-enzyme levels and hypothesize that the mechanism for this toxicity may to some part converge with the mechanism for the induction of tiredness/lethargy. Further insight into the kinetics and toxicity of interferon could provide a basis for the development of more effective, and less toxic, biological response modifiers for the treatment of renal cell carcinoma.

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