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Continuous Intravenous Interleukin-2 Infusion and Subcutaneous Interferon-α in Metastatic Renal Cell Carcinoma

Sophie D. Fosså, Håkon Aune, Eva Baggerud, Turid Granerud, Arne Heilo and Liv Theodorsen

In a phase II trial patients with metastatic renal cell carcinoma (MRCC) received two induction cycles each consisting of 24-h intravenous infusions of interleukin-2 (IL-2) 18 × 10^6 U/m^2/day and interferon (IFN) 3 × 10^6 U/m^2/day given subcutaneously on days 1–5 and 8–12 of a 2-week cycle. Between cycles 1 and 2 there was a 3-week treatment-free interval. Maintenance therapy consisted of four monthly cycles of IL-2 and IFN. Due to considerable toxicity the trial was prematurely closed after inclusion of 16 of 23 scheduled patients. Three partial responses were observed. Nine events of severe or life-threatening side-effects occurred and 8 patients were transferred to the intensive care unit. The combination of continuous intravenous high-dose infusions of IL-2 and subcutaneously given IFN is moderately effective, but too toxic for routine treatment of MRCC.
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INTRODUCTION

IN METASTATIC renal cell carcinoma (MRCC) immunotherapy with recombinant interferon-α (IFN) and/or interleukin-2 (IL-2) has yielded response rates of about 10–40% [1–8]. We present the results of a phase II study evaluating intravenous and subcutaneous IFN in MRCC and discuss why the trial was closed prematurely after inclusion of 16 patients.

PATIENTS AND METHODS

Treatment schedule

16 patients with measurable MRCC (Table 1) were entered into a phase II study evaluating the efficacy of continuous IL-2 infusions (Proleukin, EuroCetus BV, Amsterdam, The Netherlands) and subcutaneously applied IFN (Roferon, Hoffman LaRoche, Basel, Switzerland).

The treatment schedule is shown in Table 2. Three weeks after discontinuation of the two induction cycles maintenance treatment was started in non-progressing patients who did not experience unacceptable toxicity. Maintenance treatment consisted of four monthly 5-day continuous infusions of IL-2 and subcutaneous IFN (doses identical with those from cycle 1A). IL-2 was infused by an indwelling catheter inserted in the vena subclavia.

Response evaluation

Response evaluation [9] was at 3 weeks after cycle 2. Patients receiving < two cycles were deemed to be evaluable for response if they had received at least 50% of the planned dose of cycle 1.

Toxicity

Body temperature, blood pressure and the patient's weight were checked twice daily. Up to 4 g of paracetamol could be given daily to control fever and muscle pain. Hypotension (systolic blood pressure < 90 mmHg) was to be treated by interruption of the IL-2 infusion, by fluid and albumin application and, eventually, by dopamine. Blood cell counts and biochemical liver and kidney function tests were performed

Table 1. Patients' characteristics

No. of patients	16
Median age in years (range)	52 (34–68)
Male/female	12/4
Interval between diagnosis and trial entry in months (range)	23 (1–224)
Nephrectomy	15
Performance status	
0	10
1	6
Site(s) of indicator lesion(s)	
1 site	9
> 1 site	7
Lung	13
Lymph nodes	4
Liver	4
Pleura	2
Other	4
Median haemoglobin (g/100 ml) (range)	12.2 (9.8–14.8)
Median alkaline phosphatase (U/l) (range)	203 (82–452)
Median creatinine (μmol/l) (range)	109 (80–126)

Table 2. The treatment schedule

	IL-2 18 × 10^6 U/m^2/day	IFN 3 × 10^6 U/m^2/day
Cycle 1A	Day 1–5	Day 1–5
Cycle 1B	Day 8–12	Day 8–12

Cycle 1 was repeated after a 3-week rest interval (cycle 2A and 2B).

Correspondence to S.D. Fosså.
S.D. Fosså, E. Baggerud and T. Granerud are at the Department of Medical Oncology and Radiotherapy; H. Aune is at the Department of Anesthesia and Intensive Care; A. Heilo is at the Department of Diagnostic Radiology; and L. Theodorsen is at the Central Laboratory, The Norwegian Radium Hospital, 0310 Oslo, Norway.
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before each cycle, on every other day during the drug application and 2–3 days after discontinuation of the IL-2 infusion. Toxicity was scored according to the WHO criteria [9] or evaluated as slight, moderate, severe or life-threatening, based on clinical judgment.

Patients were transferred to the intensive care unit (ICU) of the hospital whenever the systolic blood pressure remained at < 90 mmHg in spite of fluid/albumin treatment or whenever the patient's situation was no longer controllable in the setting of the routine clinical ward.

Follow-up

All patients were followed up until death or 1 June 1992.

RESULTS

Response

3 of the 16 patients are unevaluable for response as their treatment was discontinued due to cardiac toxicity grade 3 or 4 before 5 days had elapsed of cycle 1A.

Partial response was seen in 3 of the 13 evaluable patients (liver and pleural metastases: 1; lung metastases: 2; response duration 4, 6, 11 months). 4 patients showed no change at their first response evaluation and 6 patients showed progressive disease.

Compliance

A total of 38 cycles were given to the 16 patients included in the study. Only 3 patients received all four scheduled maintenance treatment cycles. 2 additional patients received two maintenance cycles. Dose reductions of IL-2 had to be performed 17 times during the 26 induction cycles planned for the 13 evaluable patients, who received from 25 to 94% of their prescribed cumulative IL-2 dose (median 73%).

Toxicity

During the infusion periods all patients had chills and high fever in spite of high doses of paracetamol (median 40,3°C; range 39.8–42.0). In 8 patients weight gains of 5–10% were observed during the IL-2/IFN therapy, and 3 patients had weight gains of > 10%. 5 patients had at least one episode of hypotension.

Gastrointestinal toxicity (nausea, vomiting, diarrhoea) was the most common clinical side-effect, followed by skin rash and cardiac complications (Table 3). 2 patients developed three episodes of septicaemia. Thrombosis of the catheterised vena subclavia and embolisation of the lung, occurred in 1 patient. 8 patients were transferred to the ICU at least once. Clinical toxicity and/or the patients' request represented the cause of permanent discontinuation of the treatment in 7 of the 16 patients.

Table 3. Clinical toxicity

	No. of events among 38 cycles		
	Moderate	Severe	Life-threatening
Diarrhoea	23		
Nausea/vomiting	8		
Skin rash	5		
Cardiotoxicity	1	2	1
Mental confusion	2		
Hypotension	2		
Dyspnoea	1	1	
Melaena		1	
Arthralgia	2		
Orchitis	1		
Thrombo-embolism			1
Septicaemia		2	1
Others	5		
Total	50	6	3

11 patients developed leucocytosis (> 12.0 × 10^9/l) at least once during their treatment. The pattern of leucocytosis in the 3 responding patients was similar to that seen in non-responders. Increase of the liver function tests as evaluated by alkaline phosphatase (ALP) and aspartate aminotransferase (ASAT) was consistently observed. Serum creatinine increased to > 150 μmol/l in 8 patients, but only 2 patients developed grade 2 nephrotoxicity. Recovery from side-effects was rapid and complete and occurred within the first week after discontinuation of treatment.

DISCUSSION

When the present trial was started our group had extensive experience with IFN in MRCC, achieving a 26% response rate without major toxicity [2]. 5 of 80 patients were alive 5 years or more after IFN treatment, 4 of them without evidence of disease. At the start of the present trial nurses and oncologists were aware of the high toxicity associated with intravenous IL-2 treatment, but were highly motivated to establish safe routines at a routine clinical ward for this type of immunotherapy. However, during the trial performance the staff's motivation and the "fighting spirit" decreased gradually, in particular among the nurses. Increasingly they expressed doubts about the ethics of continuing this trial. In addition, the selected high-dose IL-2/IFN schedule proved to be extremely resource-demanding. Due to the increasing problems among the nursing staff and the simultaneous development of probably less toxic subcutaneous IL-2 therapy [7] it was decided to close this trial before the planned 23 patients had been entered.

The 16 included patients represent a selection of good prognosis MRCC patients with a favourable general condition and limited tumour burden. Our response rate of 23% (95% confidence interval 5–54%) and a response duration of 4–11 months fit well with the observations from other studies [3–8] and is in the range of what has been observed during the less toxic and more feasible treatment of MRCC with IFN [1–2].

The observed pattern of toxicity follows that of other reports [3–8] though our rate and degree of side-effects were relatively high. This is emphasised by the fact that 8 patients had to be transferred from the routine clinical ward to the intensive care unit at least once, 3 of them due to severe cardiotoxicity. Though the majority of the general side-effects (fever, gastrointestinal toxicity, fatigue, hypotension) were scored as only slight or moderate by the medical oncologist, they had a major impact on the patient's general condition. The patient's overall psychological well-being was considerably reduced as long as he/she had to face future treatment cycles.

We conclude that the treatment with continuous intravenous IL-2 treatment and subcutaneous IFN, at the doses used in the present study, is moderately active in MRCC, but too toxic for routine treatment.

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De novo Cisplatinum Resistance Does Not Influence Cellular Radiosensitivity

Richard A. Britten and Hilmar M. Warenius

The intrinsic sensitivity to 4 MeV photons, and 62.5 MeV (p→Be$^+$) neutrons has been examined in a panel of 11 cultured human cell lines exhibiting a wide spectrum of inherent cisplatinum sensitivity. Irrespective of whether cellular sensitivities to these therapeutic agents were compared at the 10% survival level, relative to the initial portion of the cell survival curves, or to their relative rank order of response, there were no significant correlations between inherent cisplatinum sensitivity and sensitivity to either 4 MeV photon, or 62.5 MeV neutron irradiation. This data raises the possibility that the previously reported decreased radiosensitivity of human tumour cell lines with acquired cisplatinum resistance may be due to the induction of cellular processes which confer resistance to both cisplatinum and ionising radiation, rather than the selection of innately cisplatinum-resistant cells, which are collaterally radioresistant.
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INTRODUCTION

THE DEVELOPMENT of cisplatinum resistance in some human tumour cell lines (acquired resistance) is associated with a concomitant reduction in photon sensitivity [1–7]. It is currently unclear how the development of acquired cisplatinum resistance results in reduced radiosensitivity, although analysis of the radiation survival curves of these cisplatinum-resistant lines, using the linear quadratic equation suggests that in comparison to the more chemosensitive parental line, the reduced radiosensitivity of cells which have developed acquired cisplatinum resistance is primarily due to a reduction in the magnitude of the initial slope (α) [5, 6].

There is currently insufficient data to demonstrate whether the reduced radiosensitivity of these platinum-resistant cells is the direct consequence of the altered expression of a single common component in the cellular response pathways to both cisplatinum and radiation, or due to multiple genetic alterations arising from exposure to cisplatinum.

The hypothesis that the reduced photon sensitivity of human cells with acquired cisplatinum resistance is attributable to the increased expression of genes responsible for intrinsic sensitivity to both therapeutic agents would seem to be supported by the close correlation between intrinsic cisplatinum and photon resistance in early passage human tumour cell lines [4, 8].

Genetic manipulation experiments have, however, shown that the cellular responses to photon radiation, and cisplatinum can be differentially modified in radiosensitive mutant CHO cells [9, 10], suggesting that innate cellular sensitivity to cisplatinum and photon irradiation may be independently encoded. Our previous studies [7], have also failed to demonstrate a consistent association between decreased photon sensitivity and the development of acquired cisplatinum resistance in five human tumour cell lines, suggesting that photon and cisplatinum sensitivity in human tumour cells with acquired cisplatinum resistance may also be independently coded. However, the same study did demonstrate a consistent reduction in sensitivity to 62.5 MeV (p→Be) neutrons, suggesting that the reduction in neutron sensitivity in cells with acquired cisplatinum resistance could be due to the induction of cellular processes which confer resistance to cisplatinum, and collateral resistance to neutron radiation.

The differential induction of collateral resistance to 62.5 MeV (p→Be$^+$) neutrons and 4 MeV photons in cells with acquired cisplatinum resistance, also implies that the mechanisms of collateral resistance to these radiations are independent of each other, and may be subject to different regulatory processes. There is, however, no evidence as to whether the reduced neutron sensitivity of these cisplatinum-resistant cells is directly

Correspondence to H.M. Warenius at the CRC Oncology Research Unit, Department of Medicine, University of Liverpool, Liverpool L69 3BX, U.K.
R. A. Britten is at the Department of Experimental Radiotherapy, University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Box 066, Houston, Texas 77030, U.S.A.
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