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The Importance of Added Albumin During Continuous Intravenous Infusion of Interleukin-2 with Alpha-interferon

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We treated 14 patients (4 malignant melanoma/10 renal carcinoma) with a combination of continuous infusion interleukin-2 (IL-2) and subcutaneous alpha-interferon. Variable concentrations of albumin were added to the infusion of IL-2. The toxicity of this regimen seems to be related to the percentage of albumin added to the IL-2 infusion. Partial responses were observed in 3 cases. Interestingly, 1 patient's response appeared dependent on the addition of human serum albumin. The mechanism of these effects is unknown, but the use of albumin with IL-2 should be carefully investigated in future studies.
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INTRODUCTION

TREATMENT WITH either interleukin-2 (IL-2) or interferon (IFN) can occasionally induce remissions in patients with malignant melanoma or renal cancer. Laboratory data indicate that the combination of these two agents may be synergistic [1]. We have therefore performed a feasibility study of this combination in such patients. During the course of the study the opportunity was taken to vary the conditions of the infusion system for IL-2. Early experience had suggested that, because of adherence to the plastic infusion set, IL-2 should be administered with albumin [2]. However, the necessity for this has not been clearly demonstrated. We therefore report our experience with 14 patients, and suggest that the addition of albumin may have a significant effect on the toxicity and efficacy of IL-2.

PATIENTS AND METHODS

Patients with histologically confirmed metastatic renal cell carcinoma and malignant melanoma were entered into the study after fully informed consent had been obtained. Eligibility criteria included performance status 0-1 (WHO scale), adequate bone marrow values [white blood cells > 4.0; platelets > 100]

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Table 1. Patients' characteristics and toxicity (WHO grades)

No. (age)	Tumour	HSA	Creatinine	Bilirubin	Alk P	AST	ALT	Ggt	N/V	Temp	Skin	Muc	CVS
1 (38)	Ren	2%	3	2	2	1	1	3	0	0	2	2	2
2 (48)	Ren	2%	0	0	4	2	0	3	0	2	2	2	2
3 (51)	Ren	2%	0	0	3	0	0	3	1	2	2	2	1
4 (54)	Ren	no	0	0	0	0	0	2	0	2	1	1	1
5 (41)	Mel	no	0	0	1	1	0	1	0	2	1	1	1
6 (65)	Ren	no	0	0	0	1	1	2	2	2	1	0	1
7 (60)	Ren	no	0	0	2	2	1	4	1	0	0	0	0
8 (67)	Ren	no	0	0	1	0	0	1	0	0	0	0	0
9 (53)	Ren	no	1	0	1	1	1	3	1	1	1	1	1
10 (58)	Ren	no	0	0	0	0	0	0	0	2	0	0	1
11 (51)	Ren	no	0	0	2	3	3	2	1	1	0	0	0
12 (43)	Mel	no	0	0	3	1	1	3	0	2	0	0	0
13 (61)	Mel	no	0	0	0	1	1	0	0	1	1	0	0
		0.2%	0	0	1	1	2	3	0	2	2	1	0
14 (44)	Mel	no	0	0	0	0	0	3	0	2	1	0	0
		0.2%	0	0	3	0	0	4	0	2	2	1	0

Ren = renal carcinoma, Mel = melanoma, Alk P = alkaline phosphatase, AST = aspartate transaminase, ALT = alanine transaminase, Ggt = gamma glutamyl transferase, N/V = nausea and vomiting, Temp = fever, Muc = oral mucositis, CVS = cardiovascular/capillary leak syndrome.

and hepatic (bilirubin within normal range) and renal (creatinine within normal range) function. 14 patients were entered; their characteristics are summarised in Table 1. Pretreatment evaluation included a physical examination, ECG and chest X-ray and tumour imaging as necessary. During therapy, vital signs were recorded at least 4-hourly, and weight twice daily. Biochemical and haematological indices were performed thrice weekly on treatment and weekly between courses. Evaluation of tumour response was carried out at approximately 4-week intervals, and toxicity was recorded according to WHO grades.

IL-2 was supplied by Eurocetus UK and was made up daily with the stated percentage of human serum albumin (HSA) (Table 1) in a solution of 5% dextrose. Each infusion was freshly made in 48 ml and infused over 24 h by syringe driver. It was administered through an indwelling central venous catheter at a dose rate of 18×10^6 IU/m^2 per day (3×10^6 CETUS U/m^2 per day) as a continuous 120-h infusion with subsequent 2 days' rest on weeks 1, 2, 9 and 10. IFN was administered by subcutaneous injection of 3×10^6 U/m^2 per day three times weekly for a total of 10 weeks.

RESULTS

The results are summarised in Table 1. Toxicity with 2% HSA was considerable in the first 3 cases with a combination of hepatic and/or renal toxicity plus a moderate degree of capillary leak. Although no patient required any pressor support, this combination of toxicities was considered unacceptable for a general ward setting. On the evidence of literature reports of only mild toxicity [3, 4] with this dose of IL-2 in the absence of albumin, it was decided to omit this in the next 9 cases. In the last 2 patients 0.2% HSA was reintroduced for the second 2 week cycle of IL-2 following progression of disease at cycle 1 (with no HSA). In 1 [13] this resulted in a dramatic response which is continuing at 7 months after therapy, with toxicity intermediate between 2% and no HSA. 2 patients (4 and 11) had stable disease for 2 and 3 months, respectively. 3 patients (3, 9 and 13) had partial responses with durations of 10+, 11+ and 7 months, respectively.

DISCUSSION

At the time of this study, no specific guidelines existed as to the use of albumin in IL-2 infusions. Since then *in vitro* investigations have led to a recommendation by the suppliers that 0.1% HSA be added if the final concentration of IL-2 is less than 100 μg/ml or 1.8×10^6 IU/ml. The object of this study was to assess the feasibility of this regimen, rather than to specifically investigate the role of albumin. *In vitro* studies have in the intervening period demonstrated a significant effect of the addition of albumin to the biological effect of IL-2 [2].

The preliminary response experience and toxicity profile in this study are similar to those in the literature. Although the numbers in this study are low we suspect that the addition of HSA does have a significant effect on the biological activity of IL-2 when given as an intravenous infusion, and this phenomena has been noted by other groups. (E.M. Rankin, Netherlands Cancer Institute, Amsterdam, The Netherlands). This was particularly evident in the last 2 patients in our series (Table 1).

Studies using the combination of IL-2 and interferon currently are focussing on subcutaneous administration, but in interpreting results from earlier studies it is important to take into consideration the use of HSA in the treatment protocol.

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