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Eur J Cancer, Vol. 27, No. 12, pp. 1613–1616, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00
Pergamon Press plc

Haemodynamic Effects of Recombinant Interleukin-2 Administered by Constant Infusion

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Adoptive immunotherapy with recombinant interleukin-2 (rhIL-2) has been reported to induce tumour regression in some patients with refractory cancer. However, the cardiovascular toxicity of bolus therapy requires invasive monitoring of patients in the intensive care unit (ICU). In an effort to examine the haemodynamic alterations caused by a constant infusion of IL-2, as opposed to bolus therapy, we studied the haemodynamic variables of 10 patients, with no evidence of heart disease, receiving 3 × 10^6 IU/m^2 per day of rhIL-2 as a continuous infusion for 5 days. Measured and derived haemodynamic variables were obtained immediately prior to, at 2, 24, and 48 h during, and upon termination of the infusion. There was no evidence of clinical haemodynamic instability in these patients. Except for development of fever and tachycardia, there were no clinically significant differences in any measured or derived haemodynamic parameter. Moreover, continuous electrocadiographic monitoring of these patients during the infusion did not reveal any abnormalities. Invasive haemodynamic monitoring in an ICU is not necessary in carefully selected patients receiving constant infusion rhIL-2, at the described dose and schedule.
Eur J Cancer, Vol. 27, No. 12, pp. 1613–1616, 1991.

INTRODUCTION

ADOPTIVE IMMUNOTHERAPY with recombinant human interleukin-2 (rhIL-2) is currently being investigated for a number of malignancies. Responses have been seen in refractory cancers, such as malignant melanoma and renal cell carcinoma [1–4]. Severe cardiovascular toxicity requiring intensive care unit (ICU) management may limit its clinical application when administered on an intermittent high dose bolus schedule [1–14]. Recent investigations suggest that dose-limiting haemodynamic instability may be attenuated when rhIL-2 is administered by constant infusion [4, 15–21]. This report describes the cardiovascular responses to high dose rhIL-2 administered by constant infusion in 10 patients.

PATIENTS AND METHODS

10 patients with advanced cancer were studied. The eligibility criteria for the trial included: age 18–70 years; metastatic or unresectable melanoma or renal cell carcinoma; expected survival of greater than 16 weeks; Karnofsky performance status 80% or higher; serum creatinine 2.0 mg/dl or less, adequate

hepatic function (aspartate aminotransase ≤ 150 IU and serum bilirubin ≤ 1.6 mg/dl); partial thromboplastin time 1.5 or lower times control; prothrombin time 1.5 or lower times control; haemoglobin 10.0 gm/dl or higher; absolute granulocyte count 1500/μl or more; platelets 100 000/μl or more; and serum calcium 12.0 mg/dl or less. All patients were required to give signed informed consent. Exclusion criteria included: presence of central nervous metastasis or underlying seizure disorder; history or evidence by cardiac stress testing of significant cardiac dysfunction; evidence of clinically significant pulmonary dysfunction; prior treatment with rhIL-2; prior biological/therapy, radiotherapy, or chemotherapy within 4 weeks of entry on study (6 weeks for nitrosoureas); clinically significant ascites or pleural effusions; and, major surgery or steroid therapy in the 3-week interval prior to entry on the study. The trial had prior approval of the Institutional Review Board of Memorial Hospital.

Treatment plan

All patients received a continuous infusion of rhIL-2 (Hoffmann-LaRoche, Nutley, New Jersey) at 3×10^6 U/m^2 per day (3×10^6 IU/m^2 per day) in 250 ml normal saline intravenously for 5 consecutive days, with paracetamol 650 mg orally or rectally, every 4 h. Diphenhydramine 50 mg every 4 h, prochlorperazine 10 mg every 4 h, meperidine 25–50 mg every 2 h or morphine 4–6 mg every 2 h were administered intravenously, as needed, for anxiety, nausea or vomiting and chills or rigors, respectively. Diphenoxylate HCl 2.5 mg and atropine sulphate 0.025 mg orally every 4 h was also administered for diarrhoea, if needed. Patients chronically receiving oral opioid analgesics or nonsteroidal inflammatory agents were maintained on their medication(s). Patients received no other medication during the study period. Patients again received rhIL-2 on days 13–17, 21–24 and 28–31. Patients underwent plasmapheresis on days 7, 8, 9 and lymphokine-activated killer (LAK) cells were reinfused on days 13, 14 and 15.

Intravenous fluids other than those needed for medications were not administered. Patients were kept on regular diets. Organ ischemia, such as decreased urine output, was treated with either 25% or 5% albumin or an increase in intravenous maintenance fluids.

Clinical and haemodynamic monitoring

Patients were admitted to the Memorial Hospital special (intensive) care unit (SCU). Through the subclavian vein, a flow-directed pulmonary artery catheter was inserted using a modified Seldinger technique. Measured and derived haemodynamic variables were obtained prior to and 2 h after the initiation of the rhIL-2 infusion in all 10 patients, and again, at 24 and 48 h in the first 5. Pulmonary artery catheters were removed after 48 h in the first 5 patients and after 2 h in the next 5.

Intracardiac filling pressures were displayed on Seimens Sirecust model 404 monitors with mercury calibrated Trantec disposable pressure transducers set with the zero reference at heart level. Right atrial (RA), systolic and diastolic pulmonary artery (PAS and PAD) and pulmonary artery occlusion pressures (PAOP) were obtained directly from the oscilloscopic screen at end-expiration using the Siemens cursor planimetry feature. Mean pulmonary artery pressure (PA) was the measured value taken from the digital display of the monitoring equipment. Cardiac output was measured in triplicate by thermodilution technique (5 ml O°C saline). Mean systemic blood pressure (BP) was calculated from the auscultatory BP. Standard formulae were used for calculations of derived haemodynamic data.

Vital signs (heart rate, blood pressure, temperature, respirations), and fluid input and output were recorded at least every 4 h. Weight was recorded daily. While in the SCU all patients were on cardiac monitors. Upon removal of the pulmonary artery catheters, patients either remained in the SCU or returned to the general medical oncology floor. Prior to termination of the rhIL-2 infusion all patients had the pulmonary artery catheter re-introduced. Haemodynamic variables were again measured immediately upon termination of the infusion at 120 h.

Statistical analysis

Measured and derived haemodynamic variables at baselines, 2 h, 24 h, 48 h and 120 h were statistically evaluated using one-sided ANOVA. Where ANOVA revaled $P < 0.05$, the paired Student's *t*-test was performed between groups. The Bonferroni method was used so that testing was at the $0.05/k$ level of significance, where k is the number of points tested.

RESULTS

10 consecutive patients, 7 men and 3 women, with a median age of 44 years (range 30–62) were entered on the trial, and haemodynamically monitored. 5 had metastatic melanoma and 5 had metastatic renal cell carcinoma. 1 patient was chronically receiving sulindac for a herniated lumbar disc. No other patient received nonsteroidal anti-inflammatory medication.

Haemodynamic monitoring

Measured and derived haemodynamic variables are shown in Table 1. The first 5 patients entered on the protocol remained in the SCU, with a pulmonary artery catheter *in situ*, for 48 h of rhIL-2 therapy. There were no untoward cardiovascular consequences to the infusion, nor were there any statistical differences in measured and derived haemodynamic variables at 2, 24 and 48 h in these patients. The next 5 patients had the pulmonary artery catheter removed after 2 h of rhIL-2 infusion, and were then discharged from the SCU.

All patients were febrile and tachycardic at the termination of the infusion (120 h), in contrast to the absence of fever and tachycardia prior to and 2 h after the initiation of therapy. During the SCU stay, continual electrocardiographic (ECG) monitoring revealed only sinus tachycardia; no ectopic beats or rhythm abnormalities were noted in any patient. No patient complained of shortness of breath, chest pain or palpitation. One patient with lung metastases developed localised wheezing over the region of lung involvement. Clinically important weight gain and/or haemodynamically significant hypotension were not encountered. 1 patient received furosemide 20 mg intravenously on the fourth day for a weight-gain of 4 kg over a baseline weight of 116 kg, associated with scant urine output. All patients experienced significant diarrhoea, requiring pharmacological intervention, by the end of the infusion. 2 patients received additional intravenous fluids due to decreased BP and falling urine output. No patient required vasoactive pharmacological support.

Cardiac index (CI), BP, left and right ventricular stroke work

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Revised 26 June 1991; accepted 17 July 1991.

Table 1. Measured and derived haemodynamic variables

	Baseline (n = 10)	2-h (n = 10)	24-h (n = 5)	48-h (n = 5)	120-h (n = 10)
HR	88 (59) ‡	87 (4) ‡	101 (7)	101 (4)	115 (5)
BP	92 (4)	89 (3)	85 (3)	76 (3)	87 (4)
RA	4 (1)	5 (1)	3 (1)	2 (1)	5 (1)
PA	13 (1)	11 (1) ‡	12 (1)	11 (2)	17 (1)
PAS	21 (1)	20 (2) †	23 (2)	21 (3)	26 (2)
PAD	9 (1) *	7 (1) †	9 (1)	5 (1)	13 (1)
PAOP	7 (1)	6 (1) †	6 (1)	3 (1)	10 (1)
CI	4.0 (0.2)	4.2 (0.3)	4.2 (0.1)	4.5 (0.4)	4.2 (0.5)
SI	46 (3) ‡	48 (3) ‡	43 (3)	44 (3)	37 (4)
SVRI	1809 (129)	1663 (104)	1543 (149)	1356 (92)	1774 (270)
LVSWI	58 (5)	58 (4)	50 (5)	46 (5)	43 (5)
PVRI	136 (16)	108 (12)	123 (19)	153 (28)	166 (29)
RVSWI	8 (1)	7 (1)	7 (1)	7 (1)	9 (1)
Temp °C	36.9 (0.01) ‡	36.9 (0.01) †			38.6 (6.0)
Weight (kg)	77.7 (5.7)				78.0 (6.0)

Mean (S.E.).
* $P \leq 0.015$ vs. 120 h, † $P \leq 0.01$ vs. 120 h, ‡ $P \leq 0.001$ vs. 120 h.
HR = heart rate (beat/min), BP = mean systemic blood pressure (mmHg), RA = mean right atrial pressure (mmHg), PA = mean pulmonary artery pressure (mmHg), PAS = systolic pulmonary artery pressure (mmHg), PAD = diastolic pulmonary artery pressure (mmHg), PAOP = pulmonary artery occlusion pressure (mmHg), CI = cardiac index (L/min/m^2), SI = stroke index (ml/beat/m^2), SVRI = systemic vascular resistance index (dyne sec/cm^5/m^2), LVSWI = left ventricular stroke work index (gm/beat/m^2), PVRI = pulmonary vascular resistance index (dyne sec/cm^5/m^2) and RVSWI = right ventricular stroke work index (gm/beat/m^2).

indices and pulmonary and systemic vascular resistances were not significantly affected. Stroke index declined, consistent with a stable cardiac output at increase heart rate. Statistically significant differences in pulmonary artery pressures and PAOP were demonstrated; however, these differences were within normal limits and were not clinically relevant. Of note, 5 patients had a decline in CI after 120 h of infusion while 5 had an increase (range of change: 53% increase to 38% decline). However, as a group, CI rose 0.2 (S.E. 0.4) l/m^2 (6–11%) by the fifth day. Changes in cardiac function did not relate to disease, age or febrile response. 1 patient developed treatment-related hepatitis resulting in lethargy, decreased oral intake and diarrhoea. He remained in the SCU after the scheduled day 5 cardiac function reassessment. His cardiac output had decreased with low intracardiac filling pressures, a marked increase in systemic vascular resistance and a borderline BP. These haemodynamic abnormalities quickly corrected with colloid and crystalloid administration and termination of the rhIL-2 infusion.

7 of the 10 patients received an additional 3 weeks of rhIL-2 infusion as described above, 4 with re-infusion of autologous LAK cells. All patients were monitored in the SCU during their first infusion of LAK cells and transferred back to the oncology floor after 24 h. No untoward haemodynamic events occurred in any of these patients. 3 patients did not complete the therapy on the protocol. 1 of these 3 with metastatic renal cell carcinoma required SCU admission and mechanical ventilation for acute respiratory failure, associated with fever and an infiltrate on the chest radiograph. The exact aetiology of this acute event was never clearly identified, although repeat right heart catheterisation revealed no difference from baseline studies. The A-a gradient was normal, and all bacteriological studies were negative.

DISCUSSION

Adoptive immunotherapy involving the administration of rhIL-2 with or without LAK cells may prove to be effective in the therapy of otherwise fatal malignancies. When administered as high-dose bolus therapy, cardiopulmonary toxicity has been dose-limiting. Hypotension requiring vasoactive pharmacological intervention, myocardial infarction, respiratory failure and significant weight gain as a result of "capillary leak" is a frequent occurrence with bolus doses of 100 000 U/kg [1–3, 5–14]. The haemodynamic pattern seen in this population is similar to that seen in septic shock with a high CI, decreased BP and low systemic vascular resistance. The need for ICU management has lead investigators to seek safer methods of rhIL-2 administration.

The $t_{\frac{1}{2}}$ elimination of rhIL-2 was just under 2 h. Administration of high doses by constant infusion results in sustained serum rhIL-2 levels with the potential for greater tumoricidal activity and attenuation of the toxicity resulting from the high peak levels seen with bolus therapy. West and associates reported toxicity in 40 patients receiving rhIL-2 (Cetus) at 3.0×10^6 U/m^2 per day (18×10^6 IU/m^2 per day) for 5 consecutive days. 6 of 40 patients required ICU transfer during their treatment; 5 of 6 patients were observed for periods of significant hypotension. 14 patients were hypotensive, most commonly after LAK cell infusion, 5 of whom required low-dose dopamine administration [4].

In our carefully selected patient population, all of whom had an excellant performance status and no antecedent cardiopulmonary disease, rhIL-2 administered at 3.0×10^6 IU/m^2 per day by constant infusion was not associated with significant haemodynamic instability. 10 patients treated with the aid of a right heart catheter exhibited no significant clinical alterations

other than development of tachycardia and fever. Changes in measured haemodynamic parameters (elevation of PA, PAS, PAD, PAOP and decrease in SI) were of no clinical consequence. Infusion of vasoactive agents was not necessary. Localised bronchospasm occurred in 1 patient in an area of metastatic disease and may have been due to tumour swelling with rhIL-2 therapy.

Since no significant cardiovascular morbidity was observed in the 10 monitored patients, an additional 33 patients were treated on the same protocol on the general oncology floor. 2 of the 33 patients developed supraventricular tachycardia, and 1 experienced myocardial infarction. This incidence of myocardial infarction and arrhythmias in our patients (7%) was not significantly different from the 13.25% ($P = 0.06$) reported by Lee *et al.* [5] using high-dose bolus rhIL-2. However, 65% of the patients (277/317) reported by Lee *et al.* needed vasoactive medication for BP maintenance versus none in this series. Thus, although this dose and schedule decreases the incidence of hypotension and the need for pharmacological intervention, acute myocardial infarction and supraventricular arrhythmias can still occur in patients with no antecedent cardiac history. Therefore, careful observation is warranted in all patients receiving rhIL-2, but it can be conducted in a non-ICU setting in those receiving infusional therapy. Two potential variables may explain the decreased haemodynamic toxicity noted in this study. Firstly, the patient population was relatively young. Secondly, the dose of rhIL-2 was less than that used in other trials, especially accounting for the biological equivalence of rhIL-2 products. Although the dose of rhIL-2 used was 3.0×10^6 IU/m^2 per day intravenously, the biologically equivalence of the recombinant product was less than that of the rhIL-2 used in the trial reported by West *et al.* [4].

The precise mechanism for the cardiopulmonary toxicity during high-dose bolus administration or constant infusion has not been determined. It may be related to a direct effect of the rhIL-2 or LAK cells, or may be mediated by other factors such as other lymphokines (gamma interferon, tumour necrosis factor), complement activation, myocardial oedema, unidentified myocardial depressant factors or free radical formation [5, 6, 14]. This toxicity appears more intense with LAK cell re-infusion [14]. This study reflects only the haemodynamic findings of rhIL-2 during the "primary" phase of the protocol and dose not examine the haemodynamic effects of rhIL-2 plus LAK cells.

In conclusion, rhIL-2 administered by constant infusion at this dose and schedule does not require invasive monitoring. However, serious toxicity, such as myocardial infarction and supraventricular arrhythmias may occur and is unpredictable. Until the exact mechanism(s) of cardiac toxicity is elucidated or baseline screening tests can predict their occurrence, rhIL-2 therapy should be restricted to carefully selected cancer patients with a good performance status and no underlying cardiopulmonary disase. ICU admission for haemodynamic monitoring is not necessary with constant infusion rhIL-2; non-invasive cardiac monitoring may, however, be prudent at the time of LAK cell re-infusion.

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