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Multiple organ failure during interleukin-2 administration and LAK cells infusion

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Abstract. Adoptive immunotherapy is a new promising treatment for cancer but is associated with severe toxicity mainly related to a capillary leak syndrome. We report the case of a patient with metastatic hypernephroma, who had many complications such as coma, renal failure, pulmonary edema, life-threatening acidosis, cardiac arrhythmias and venous thrombosis. Critical care specialists should be aware of this type of cancer therapy because of multiple side effects requiring ICU supportive care.

Key words: Immunotherapy – Cancer – Interleukin-2 – Capillary leak syndrome

Adoptive immunotherapy (AI) with interleukin-2 (IL-2) and lymphokine-activated killer (LAK) cells infusion is a new therapeutic approach to cancer. Although still investigational, this approach, first described by Rosenberg [1], appears to be very promising. However, it can be associated with severe toxicity, mainly related to a capillary leak syndrome [1].

Case report

A 58-year-old man with a hypernephroma had a nephrectomy 2 years before, developing metastatic disease in bones and lungs. On admission he complained only of mild pain in the right hip. Extensive investigation was otherwise negative. Creatinine clearance was 75 ml/min. Recombinant human IL-2 (provided by Ortho Pharmaceutical Corp., Raritan, New Jersey, USA) was given intravenously in a dose of 30000 U/kg every 8 h from days 1 to 5 as well as cimetidine (400 mg bid, p.o.), indomethacin (25 mg tid, p.o.) and paracetamol (500 mg q4h, p.o.). The patient developed erythroderma, purpura, diarrhea, mild renal failure (Table 1) and fluid retention with a gain of body weight of 8 kg. Leukapheresis were performed daily from days 8 to 12. The collected cells were incubated 3–4 days with IL-2 to allow ex vivo expansion of the LAK cells. LAK cells were reinfused on days 12, 13 and 15 and IL-2 was given back on day 12 at the same dosage. On day 15, oliguria, hypotension (systolic B.P.: 75 mmHg) and increase of creatininemia lead to discontinuation of IL-2 treatment after the last LAK cell infusion. The patient developed severe dermatitis, eosinophilia, and diarrhea. He became anuric. Furosemide and low dose dopamine (2 mcg/kg/min) were given. On day 16, he was unconscious. Serum creatinine increased to 6.2 mg/100 ml. On day 18, he received ventilatory assistance because of severe acidosis; high doses of corticoids were administered and diuresis started again. Consciousness progressively improved. On day 19, atrial fibrillation and acute pulmonary edema (Fig. 1) compatible with ARDS occurred. PEEP was initiated. On day 25, a deep venous thrombosis of the right leg, probably related to low antithrombin III and protein C levels (Table 1) in the blood, was treated with heparin. The patient was extubated on day 26 but, 2 days later, developed severe hypercapnia and ventricular fibrillation, requiring reintubation. He was again extubated on day 29 but relapsed with a cardiac arrest on the following day. He was left on ventilatory support until day 47 and discharged on day 52. At that time, he had severe amyotrophy but presented an objective antitumor response with complete disappearance of the lung metastasis and partial regression of the bone metastasis.

Discussion

This case is remarkable by the number of complications induced by IL-2 treatment. Chills and fever, dermatitis, diarrhea, weight gain, oliguria, hypotension, renal failure and thrombopenia are frequent complications of AI with IL-2 [1]. In Rosenberg's experience, about 20% of the patients develop respiratory distress because of pulmonary edema and half of them had to be intubated; cardiac arrhythmias and CNS toxicity

Table 1. Evolution of biological parameters during and after treatment with interleukin-2

Parameter	Normal range and limits	Day of treatment									
		1 (baseline)	6	12	14	16	18	19	25	28	50
Proteinemia	6.0 – 7.5 mg/100 ml	5.9	3.6	5.5	4.3	5.1	4.6	5.4	4.9	5.5	6.5
Creatinemia	0.7 – 1.5 mg/100 ml	1.1	2.9	1.3	2.4	5.5	6.2	5.8	1.3	2.0	1.3
SGPT	≤ 20 mU/ml	9	44	23	21	21	14	15	13	14	25
CRP	0.1 – 5.0 mg/100 ml	5.6	15.6	2.6	20.4	30.7	ND	ND	7.8	ND	1.7
Hemoglobinemia	12 – 18 mg/100 ml	14.1	10.3	11.0	10.5	9.5	8.9	10.1	9.7	10.1	10.1
Platelet	$140 - 440 \cdot 10^3/mm^3$	269	32	137	156	220	ND	94	83	195	219
White cell	$4300 - 10000/mm^3$	8300	7500	12300	13100	5800	ND	14300	20200	7900	17000
Eosinophils	1 – 6%	2	0	6	ND	46	ND	ND	3	ND	1
Antithrombin III	70 – 125%	113	49	95	ND	28	22	ND	70	ND	102
Protein C	70 – 130%	106	26	60	ND	28	< 25	ND	ND	ND	113
pH		7.38	7.34	7.37	7.28	7.28	7.07	7.34	7.39	7.02	7.41
PaO_2	mmHg	92	96	ND	92	93	67	69	116	53	79
$PaCO_2$	mmHg	38	29	ND	29	28	62	38	34	68	36
Lactatemia	< 2 mMol	2.1	4.3	2.0	2.0	1.7	2.8	3.4	2.0	5.0	1.0

ND = not done

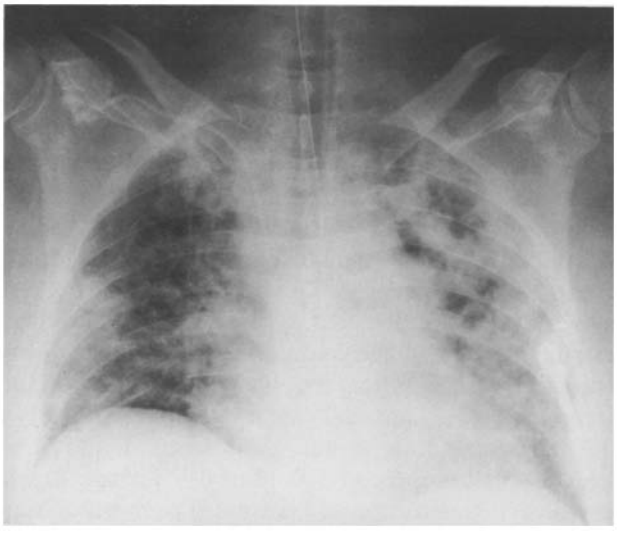

Fig. 1. Chest X-ray performed on day 19 of the treatment and showing diffuse pulmonary edema

(somnolence, desorientation, coma) are not rare either. IL-2 toxicity is mainly due to a capillary leak syndrome mediated by host lymphoid elements [2]. This side effect is dose-related and can experimentally be prevented by immunosuppression. Corticosteroids [3] can reduce fluid retention and decrease IL-2 lethality but they are detrimental to the antitumoral activity of LAK cells. In a few cancer patients treated by IL-2 and corticosteroids [4], side effects were significantly decreased and fluid retention was delayed. IL-2 induces a hemodynamic pattern similar to that seen with septic shock, with increased cardiac index and decreased systemic vascular resistance [5]. Renal toxicity with azotemia and oliguria is more severe in patients with pretherapy serum creatinine values above 1.4 mg/100 ml and with nephrectomy, as in our case [5]. We have documented a strong decrease in antithrombin III and protein C levels, probably by synthesis inhibition, that can explain the occurrence of deep vein thrombosis. Finally, severe acidosis could be related to a hypermetabolic status induced by activation of a cascade of immune cells with liberation of various cytokines.

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