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Pulmonary toxicity of recombinant interleukin-2 plus lymphokine-activated killer cell therapy

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Pulmonary toxicity of recombinant interleukin-2 plus lymphokine-activated killer cell therapy. F. Villani, M. Galimberti, M. Rizzi, R. Manzi. ©ERS Journals Ltd 1993.

ABSTRACT: The aim of the present investigation was to evaluate lung toxicity in 15 patients affected by metastatic melanoma of different sites, and treated with recombinant interleukin-2 (rIL-2) plus lymphokine-activated killer (LAK) cells.

The treatment regimen included a first and a second course of rIL-2, separated by four consecutive daily leukaphereses. Autologous LAK cells were reinfused during the second course. Lung function was monitored before and after each rIL-2 administration.

In the 12 patients who could be followed until completion of the therapy, spirometric parameters and transfer factor of the lungs for carbon monoxide (T_{LCO}) decreased significantly during the first rIL-2 course, remained stable during leukapheresis, and declined significantly further during the second rIL-2 course. In the second phase, chest radiography documented some degree of pulmonary oedema, ranging from interstitial oedema to frank pulmonary oedema. A significant dose-dependent correlation was found between the cumulative rIL-2 dose and the decline in T_{LCO} in the first course of therapy. Moreover, patients who developed symptomatic respiratory insufficiency (World Health Organisation grade III or IV) during the second course of therapy received a higher number of LAK cells than those who did not.

The data support the hypothesis that LAK cells have an additional toxic effect on the lung.

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The administration of recombinant interleukin-2 (rIL-2) and lymphokine-activated killer (LAK) cells has been recently found to induce regression of metastatic cancer in animal [1], and human immunotherapy trials [2, 3]. Objective responses have been observed in a fraction of patients with different tumour types, including melanoma, renal carcinoma, colorectal carcinoma and non-Hodgkin's lymphoma [3–6]. The administration of rIL-2 is associated with side-effects involving multiple organ systems and, in particular, renal, hepatic, cardiac, haemodynamic and respiratory toxicity has been described [2–4, 7–9]. Pulmonary dysfunction is relatively frequent, and is characterized by the development of respiratory insufficiency, which sometimes requires supplemental oxygen administration, and in some cases additional temporary intubation [8, 10, 11]. However, the contribution from LAK cell infusion to lung function changes is controversial.

Preliminary studies seem to indicate that injection of a large number of activated lymphocytes can be performed without the occurrence of significant toxicity [12, 13]. More recently, it was demonstrated in an animal model that a LAK cell population can mediate a vascular leak syndrome in the lung, which is considered a prominent aspect of lung toxicity [14].

Therefore, to further characterize the pulmonary changes associated with rIL-2 alone, and with rIL-2 plus LAK cell administration, we prospectively monitored 15 patients during the first cycle of treatment with rIL-2 alone and during the second course of rIL-2 associated with LAK cell administration.

Patients and methods

Patients

The study was conducted on 15 patients, suffering from melanoma, with measurable lesions in the lungs, liver, subcutaneous tissue or lymph nodes. Their mean age was 46 yrs (range 22–59 yrs), and all had a performance status >70 (Karnofsky) upon entry into the study. There were 11 males and 4 females. There was no evidence of major liver, kidney or heart dysfunction. Bone marrow reserve was normal (World Health Organization (WHO) grade 0 for baseline values of white blood cells, granulocytes, platelets and haemoglobin). No anticancer treatment had been administered during the four weeks preceding rIL-2 administration. No patient had any pretreatment history of asthma, bronchitis or chronic obstructive lung disease.

Drug

The rIL-2 used in the study was a sterile lyophilized powder (Glaxo, Geneva, Switzerland). It has a molecular weight of about 15,000 Da, is composed of 133 amino acids, and has a specific activity of about 2.3×10^6 U·mg^{-1} of protein compared with the standard form from the US Biological Response Modifiers Programme.

Drug administration

The treatment regimen consisted of two courses of rIL-2 injections, separated by four consecutive daily leukaphereses. Patients received 400 mg·m^{-2} of rIL-2 by *i.v.* bolus injection three times daily, for 4–6 consecutive days. The duration of the first cycle was planned to achieve lymphocyte rebound. After the first course, leukapheresis was performed daily for four consecutive days, starting 24–30 h after the last rIL-2 administration. Daily leukapheresis lasted about 5 h, during which time 11–15 *l* of whole blood were processed. Lymphocytes from each leukapheresis were grown *in vitro*, and activated *ex vivo* with rIL-2 for 3–4 days, as described previously [15]. In the second course, rIL-2 was administered at the dose of 400–800 μg·m^{-2} by *i.v.* bolus injection for 7 consecutive days, starting from the day after the last leukapheresis. Autologous LAK cells were reinfused into each patient three times (on the 1st, 2nd and 4th day) during the second course of rIL-2 administration. During the second course of treatment, all patients were kept in the Intensive Care Unit. Patients were also monitored throughout the study for hepatic, renal, haematological and metabolic abnormalities.

Lung function tests

Lung function was evaluated by means of blood gas analysis and spirometry and by determining transfer factor of the lungs for carbon monoxide (TLCO). Patients were also submitted to chest X-ray. Standard spirometric parameters were determined using a Sensor Medics (Yorba Linda, California, USA) spirometer (model PFT 5 Horizon Systems), and were expressed as percentages of European Coal and Steel Community [ECSC] 1983 predicted values. TLCO was evaluated with the single breath technique [16], and TLCO was corrected for haemoglobin concentration according to DINAKARA *et al.* [17]. Lung function tests and chest X-ray were performed before the beginning of treatment, at the end of the first course of rIL-2 administration, and before and after the second course of rIL-2 injection. The degree of organ toxicity was evaluated according to WHO grading (I to IV). Only 10 patients could be checked after a follow-up of more than 7 days. Verbal informed consent was obtained from all patients before entry. The protocol was reviewed and approved by the research and Ethics Committee of the Institute.

Statistical analysis

Results are presented as mean values±standard error of the mean. Statistical evaluations were performed by using Student's t-test for paired and unpaired observations.

Results

General toxicity

All 15 patients completed the first course of rIL-2, which in four cases lasted 4 days, in five cases 5 days, and in six cases 6 days. The cumulative dose of rIL-2 ranged from 4,800–7,200 μg·m^{-2}. No reduction of the scheduled daily dose was necessary. Only six patients completed the second course of treatment, with no significant toxic effects. One patient died during the second course of rIL-2 administration from progression of disease and cardiorespiratory insufficiency. The rapid appearance of fluid retention, pericardial pleural and peritoneal effusion, pulmonary oedema and electrolyte imbalance suggests that rIL-2 may have contributed to the death, but it should be emphasized that necropsy evidenced extensive metastases in many organs, including myocardium and pericardium.

In four cases, the second course of rIL-2 administration was discontinued before the completion of therapy, because of toxicity. In two cases the rIL-2 dose was reduced and then discontinued early after the completion of LAK cell administration. In another two cases, rIL-2 therapy was stopped during the first 2 days of the second course, without completion of LAK cell infusion. The total treatment period ranged from 11–19 days, rIL-2 total dose from 5,602–15,000 μg·m^{-2}, and LAK cell total dose from $11.5–40\times10^9$ cells·m^{-2}.

All patients experienced some toxic effects of various types and severity during treatment. Only three patients had an increase in body weight of more than 10% of the treatment value. Toxic effects included fever and malaise (12 of 15 patients), gastrointestinal symptoms (emesis, diarrhoea or abdominal pain in 9 of 15 patients), hepatic (jaundice, serum glutamic oxalo-acetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) increase in 14 of 15) and renal toxicity (increase in blood urea nitrogen (BUN) and creatine in 9 of 15), neuropsychiatric reactions (behaviour abnormality, depression, confusion in 8 of 15), cutaneous toxicity (erythematous-exfoliative dermatosis in 11 of 15), haematological toxicity (anaemia, leucopenia and thrombocytopenia in 9 of 15), and cardiovascular toxicity (arrhythmia, hypotension in 5 of 15). The spectrum of organ toxicity was similar to that reported in the literature [2, 3, 7, 10]. During the first course of therapy, relatively few adverse effects were recorded, and they usually began on the second and third day of treatment. More severe toxicity was seen during the second course of rIL-2 administration.

Lung toxicity

Spirometric parameters and TLCO could be monitored before and after each rIL-2 course in 12 patients. Of the remaining three patients, one died, and two refused to be checked after completion of therapy. Total lung capacity (TLC), vital capacity (VC), residual volume (RV), forced expiratory volume in one second (FEV_1) and forced expiratory flow at $_{25-75}$% VC (FEF_{25-75}) decreased significantly during the first course of rIL-2 administration (table 1). The FEV_1/VC ratio also significantly declined, whereas the RV/TLC ratio remained stable. TLCO and transfer coefficient for carbon monoxide (TLCO/VA) also significantly decreased (table 2). Arterial oxygen tension (Pao_2) and arterial carbon dioxide tension ($Paco_2$) declined, but the change was not found to be statistically significant. During the first course of therapy, chest X-rays did not show any clear-cut pattern of interstitial oedema, or progression of the extent of pulmonary metastasis.

A significant dose-dependent correlation was found between cumulative rIL-2 dose and the decline in TLCO in the first course of therapy (table 3). In contrast, no correlation was found in the second course of therapy when rIL-2 was administered with autologous LAK cells.

Table 1. – Spirometric parameters recorded before and after each rIL-2 administration (12 patients)

	Before treatment	After 1st course	Before 2nd course	After 2nd course
TLC	108±6.3	91±4.4*	94±5.4*	91±6.0*
VC	94±4.7	90±3.6*	87±3.8*	77±4.4*
RV	141±11.0	109±8.1*	110±11.9*	104±7.1*
RV/TLC	124±3.9	115±4.6	110±6.1	125±6.4
FEV_1	97±4.7	83±15.7*	86±4.7*	74±5.1*
FEF_{25-75}	97±7.8	77±8.6*	77±6.5*	62±7.3*
FEV_1/FVC	106±2.5	101±1.8*	102±1.7*	99±2.6*

Data are presented as mean±SEM of % predicted values. *: $p<0.05$ (student's t-test for paired data). TLC: total lung capacity; VC: vital capacity; RV: residual volume; FEV_1: forced expiratory volume in one second; FEF_{25-75}: forced mid-expiratory flow; FVC: forced vital capacity; rIL-2: recombinant interleukin-2.

Table 2. – Transfer factor of the lung for carbon monoxide and TLCO/VA before and after each rIL-2 administration

	TLCO ml·min^{-1}·mmHg^{-1}	TLCO/VA ml·min^{-1}·mmHg^{-1}·l^{-1}
Before treatment	28.9±1.6	4.6±0.3
After 1st course	24.9±1.7*	4.1±0.25
Before 2nd course	25.4±1.8*	4.2±0.28*
After 2nd course	23.3±1.5*	3.9±0.3*

Data are presented as mean±SEM. *: $p<0.05$ (student's t-test for paired data). TLCO: transfer factor of the lung for carbon monoxide; TLCO/VA: transfer coefficient for carbon monoxide; rIL-2: recombinant interleukin-2.

Table 3. – Effect of different cumulative doses of rIL-2 on transfer factor of the lung for carbon monoxide (TLCO)

M Cumulative dose µg·m^{-2}	Pts n	TLCO ml·min^{-1}·mmHg^{-1} Before treatment	After 1st course	-Δ%
4873±43	3	26.1±3.8	24.5±4.0	-6.1
5834±67	6	27.2±3.8	25.0±3.6	-8.0*
7147±71	6	29.6±1.2	23.8±1.3	-19.5**

Data are presented as mean±sem. *, **: $p<0.005$, <0.005.

Lung function tests remained stable during leukapheresis, and then significantly declined during the second course of rIL-2 administration (see table 1).

Pao_2 and $Paco_2$, which had been slightly modified after the first course of therapy, significantly changed during the second period of rIL-2 administration: Pao_2 decreased from 70±2 to 54±4 mmHg (9.3±0.3 to 7.2±0.5 kPa), $p<0.01$) and $Paco_2$ increased from 40±2 to 48±3 mmHg (5.3±0.3 to 6.4±0.4 kPa), $p<0.01$. Moreover, the respiratory rate increased significantly (>30breaths·min^{-1}). In the second phase, chest X-ray controls documented, in almost all the patients, some degree of pulmonary oedema, ranging from interstitial oedema to frank pulmonary oedema. Six patients required supplemental oxygen administration (fractional inspiratory oxygen (FIO_2) 0.3–0.4) for dyspnoea: and two required continuous positive airways pressure (CPAP) at the end of rIL-2 infusion for severe dyspnoea and marked gas analysis changes ($Paco_2$ >50 mmHg (6.7 kPa) and/or Pao_2 <60 mmHg (8.0 kPa)). Analysis of single cases showed that patients who developed significant respiratory insufficiency (WHO grade III or IV) differed from those who did not, in relation to the number of LAK cells injected, rather than to the total cumulative dose of rIL-2 (table 4). In all of these patients, dose reduction and, eventually, discontinuation of the treatment was necessary.

Radiological signs of pulmonary oedema generally resolved within 3 days of the completion of therapy, whereas amelioration of lung function parameters in the five patients who could be checked required more than 10 days.

Table 4. – Total dose of rIL-2 and LAK cells in patients with and without symptomatic respiratory insufficiency

	Pts n	rIL-2 µg·m^{-2}	LAK cells 10^9 cells·m^{-2}
Patients with RDS	6	11497±906	24.3±3.1
Patients without RDS	8	12555±836	16.6±1.9
p		NS	<0.05

rIL-2: recombinant interleukin-2; LAK: lymphokine-activated killer cells; RDS: respiratory distress syndrome.

Discussion

The results of the present study confirm that the administration of rIL-2 and LAK cells is associated with side-effects involving multiple organ systems, particularly the lung. The spectrum of organ toxicity was similar to that reported in previous studies [2, 3, 7, 10]. Pulmonary toxicity was present in all patients with different degrees of severity. In most of them (8 of 15), lung toxicity was present only at the subclinical level, and was evidenced by a significant decrease in spirometric parameters, and by a significant decline in TLCO. The restrictive nature of such a pulmonary defect is suggested by the simultaneous decrease in all expiratory air flow rates and volumes. Moreover, the significant decrease in FEV_1/VC also suggests the occurrence of an obstructive component, in agreement with the results recently reported [18].

In six patients, pulmonary toxicity was clinically relevant in the second course of therapy. All of them required supplemental oxygen administration for dyspnoea, and two required CPAP at the end of rIL-2 infusion, because of severe dyspnoea and marked gas analysis changes.

Chest radiograph findings confirmed that accumulation of water in the lung due to increased capillary permeability is the most prominent aspect of rIL-2 lung toxicity [8, 11, 19–22]. However, the recent observation by transbronchial lung biopsies that, besides septal oedema and fibrin deposition, interstitial infiltration by lymphocytes and eosinophils also occurs in rIL-2 treated patients, suggests the possibility that increased interstitial cellularity may contribute to reduced lung compliance, and induce a restrictive defect [18].

The toxic effect of rIL-2 on the lung was found to be dose-dependent, since a significant dose-dependent correlation was found between the cumulative dose of rIL-2 and the decline in TLCO in the first course, when rIL-2 was administered alone.

Lung toxicity of rIL-2 was reversible; however, whereas the radiological signs of pulmonary oedema resolved within 3–4 days, the amelioration of lung function parameters generally required more than 5 days. This is confirmed by the persistence of the restrictive defect during the leukapheresis period, which lasted 4 days, and by its time course after the completion of the second course of therapy in the few patients who could be followed for long enough (data not shown).

In contrast with the results reported by some authors [11–13], LAK cells obtained by leukapheresis and later infused into patients appear to have contributed to pulmonary toxicity. In fact, patients who developed significant respiratory insufficiency had received the same cumulative dose of rIL-2 as asymptomatic patients. In contrast, the total dose of LAK cells reinfused into patients with symptomatic respiratory insufficiency was significantly higher than that of asymptomatic patients. The hypothesis is further confirmed by the fact that in the second course of therapy, when rIL-2 was administered with LAK cells, no correlation was found between the cumulative rIL-2 dose and TLCO, in contrast to that observed in the first phase. The predilection of rIL-2-activated cells for the lung, the capacity of LAK cells to damage vascular endothelial cells, as supported by some experimental studies [23–25], and the suspected higher sensitivity of pulmonary vasculature than other tissue to cellular and biochemical agents responsible for vascular leak, may represent a toxic potential for the lung, and could explain the apparent contribution of LAK cells to the development of pulmonary toxicity observed in our study.

The cause of pulmonary toxicity of rIL-2 is not completely clarified, but it is generally attributed to the development of vascular leak syndrome. The development of increased systemic and pulmonary vascular permeability during rIL-2 adoptive immunotherapy has been substantiated in several animal models [25, 26]. The mechanism by which pulmonary oedema develops after rIL-2 therapy remains to be clarified. It is unclear whether the effect on vascular permeability is mediated directly by rIL-2, or indirectly by release of other vasoactive substances. A direct effect of rIL-2 appears unlikely, since in nude mice [22], and in animals irradiated or treated with cyclophosphamide [27], or steroids [28], rIL-2 shows less evidence of capillary leak syndrome. Moreover, it was demonstrated in an ovine model of rIL-2 toxicity that the acute endothelial dysfunction characteristic of the vascular leak syndrome is not due directly to rIL-2 [29]. More recently, it was demonstrated in an animal model that the concomitant administration of LAK cells and IL-2 produced a significant, more extensive, extravasation of fluid and albumin in the lung than after LAK cells or IL-2 alone [14]. Therefore, the most likely explanation for the vascular leak syndrome is that toxicity may be mediated by LAK cell phenomena, whether they are generated endogenously or exogenously [24, 30]. In other words, lymphocytes, activated directly *in vitro* or *in vivo*, could act through the release of vasoactive substances.

Moreover, rIL-2 may activate cells other than lymphocytes (for instance macrophages), with the release of mediators and eventual interaction between several cell types and mediators [20, 31, 32]. The mediators of lung toxicity are unknown, and need further elucidation. However, likely candidates include platelet-derived growth factor, interleukin 1, transforming growth factor-β, tumour necrosis factor-α, insulin growth factor-1 and interleukin-6 [33], various arachidonic acid metabolites, such as thromboxane and prostaglandins [21, 34–36], oxygen-free radicals [37], and interferon [38]. Finally, since rIL-2 administration is also associated with cardiac toxicity, as manifested by an increase in cardiac index and by a decline of the left ventricular stroke work index, and a decline of left ventricular ejection fraction [39], it cannot be excluded that cardiac dysfunction may also contribute to the pulmonary oedema seen in these patients, although recent experimental results seem to exclude a direct action of rIL-2 on the heart [40].

In conclusion, the results of the present study confirm that rIL-2 induces lung toxicity in the form of a restrictive defect. Such a toxic effect is dose-dependent. Moreover, the present observation supports the hypothesis that LAK cell administration has an additional toxic effect on the lung, which is mediated through a still undefined mechanism [20, 22, 40, 41]. Finally, it should be stressed that

the regimen used in these patients produced very severe side-effects and had, on the whole, an unacceptable toxicity. A lower dose regimen, or continuous exposure, are thus recommended, since they seem to preserve the antitumour activity and to decrease toxicity, thereby increasing the safety and comfort of patients [6].

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