Chest Roentgenographic Abnormalities in IL-2 Recipients

Incidence and Correlation with Clinical Parameters

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The chest roentgenograms of 54 patients receiving high dose interleukin-2 with or without lymphokine-activated killer cell therapy for advanced cancer were retrospectively reviewed. Thirty-nine patients (72 percent) developed chest roentgenographic abnormalities consisting of pleural effusions, 28 (55 percent); diffuse infiltrates (pulmonary edema), 22 (41 percent); and focal infiltrates, 12 (22 percent). These abnormalities resolved in 30 of 39 (77 percent) patients by four weeks after therapy. Simple pleural effusions were the only residual roentgenographic abnormalities seen and were present primarily in patients receiving IL-2 by bolus intravenous injection (8 of 28) (29 percent) as compared to continuous intravenous infusion (1 of 24) (4 percent) (p = 0.03). Only roentgenographic evidence of pulmonary edema appeared to correlate with the degree of clinical pulmonary toxicity (p = 0.001). The development of chest roentgenographic abnormalities correlated with the administration of IL-2 solely by bolus intravenous injection (p = 0.04), a pretreatment FEV, of less than 3 L (p = 0.04), and treatment associated bacteremia (p = 0.09), but not with prior therapy, the presence of pulmonary metastases or the degree of systemic capillary leak as measured by percentage of weight gain during therapy. Although the roentgenographic abnormalities did not relate to the number of LAK cells received, two patients developed sudden onset of dyspnea and chest roentgenographic evidence of pulmonary edema shortly after the first LAK cell administration, implying that a direct cause-and-effect relationship exists in some patients. Possible mechanisms for these IL-2 related chest roentgenographic abnormalities and pulmonary toxicity in general are discussed. (Chest 1992; 101:746-52)

Clinical trials using recombinant human interleukin-2, with or without autologous LAK cells, have yielded promising results, particularly in patients with melanoma or renal cell carcinoma. However, this treatment has also been accompanied by multiple acute but generally reversible toxic effects including fever, chills, lethargy, diarrhea, anemia, thrombocytopenia, eosinophilia, confusion, diffuse erythroderma, hepatic dysfunction, intravenous catheter related bacteremia, thyroid dysfunction, and a capillary leak syndrome leading to hypotension, fluid retention and renal insufficiency. Respiratory difficulties occasionally severe enough to necessitate intubation and assisted ventilation and cardiac dysfunction, including arrhythmias and myocardial ischemia/infarction, have also been observed.

Conant et al reported the appearance of pulmonary edema on chest roentgenograms in five of eight patients receiving IL-2 therapy with or without LAK cells. More recently, Mann et al reported on the chest roentgenographic changes during the initial five days of therapy in 19 patients receiving high-dose IL-2 and LAK cells. They also saw pulmonary edema develop in over 50 percent of patients and presented corresponding central venous pressure measurements and serum albumin levels which supported a "vascular leak" rather than hydrostatic mechanism for these IL-2-associated changes. Davis et al, using a lower dose, but more protracted IL-2 treatment regimen, observed a 46 percent incidence of pleural effusions and 21 percent incidence of pulmonary edema in 43 patients with renal cell carcinoma. No pretreatment or therapy-related risk factors for these roentgenographic abnormalities were assessed in any of these studies.

In an attempt to characterize the nature, time course, and clinical correlates of IL-2 related chest roentgenographic abnormalities, we retrospectively reviewed the chest roentgenograms of 54 patients who underwent treatment with high dose IL-2 with or without LAK cells at the New England Medical Center. We now report our observations, including clinical correlations with potential pretreatment and treatment-related risk factors, and discuss possible

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EC = endothelial cells; ELAM = endothelial leukocyte adhesion molecule; ICAM-1 = intercellular adhesion molecule-1; LAK = lymphokine activated killer.
mechanisms for the IL-2 related chest roentgenogram abnormalities and pulmonary toxicity in general.

METHODS

Study Design

Patients were treated in the Clinical Study Unit of the New England Medical Center as part of a larger, six center clinical trial of IL-2 and LAK cell therapy conducted by the National Cancer Institute Extramural IL-2/LAK Cell Working Group. All treatment protocols were designed by the National Cancer Institute and approved by the Food and Drug Administration and the Human Investigation Review Committee at the New England Medical Center. Written informed consent was obtained from each patient.

Patients were treated with IL-2 according to five schedules (Fig 1). Protocols were conducted sequentially. Two protocols (1a and 1b) involved bolus intravenous IL-2, 600,000 IU/kg every 8 h days 1 to 5 and 12 to 16 (max, 28 doses), leukapheresis days 8 to 11, and autologous LAK cell days 12, 13, and 15 in a manner essentially identical to that described by Rosenberg et al. The 20 patients receiving these two treatment regimens were combined for the purpose of this analysis. Ten patients (protocol 2) were treated with bolus injections of IL-2 alone, without LAK cells, on a schedule otherwise identical to that employed in protocols 1a and 1b.

Seventeen patients were treated according to a modified regimen (protocol 3), in which they received nine instead of 14 doses of IL-2 (days 1 to 3) before leukapheresis; four instead of five days of leukapheresis (days 5 to 8); and a continuous infusion of IL-2 (1μg/kg/h), instead of bolus injections during the period of LAK cell administration (days 9 to 15). Seven patients were treated according to a second modified protocol (protocol 4) in which IL-2 was administered by continuous infusion at a dose of 1 mg/m²/day before the leukapheresis (days 1 to 5) and during the period of LAK cell administration (days 11 to 16); and leukapheresis procedures were performed on days 7 through 10.

All patients had advanced metastatic cancer which was either refractory to conventional therapy or for which no conventional therapy existed. All patients had measurable disease, were ambulatory with an Eastern Cooperative Oncology Group performance status of 0 or 1, and had generally normal organ function. Prior to therapy, all patients were evaluated for eligibility with pulmonary function tests (PFTs), chest roentgenograms, arterial blood gases, and in most cases, exercise tolerance tests. All patients satisfied the eligibility requirements for treatment which included PFTs showing a FEV₁ greater than 2 L or at least 75 percent of predicted for patients' body size, the absence of pleural effusion on chest roentgenogram, an arterial PO₂ greater than 60 mm Hg, and no evidence of cardiac ischemia or congestive heart failure.

Chest roentgenograms were obtained immediately prior to initiating therapy, at the end of the first IL-2 course, at both the start and conclusion of the IL-2/LAK cell or second IL-2 alone course, and four weeks after completing therapy. Additional chest roentgenograms were obtained as the patient's symptoms warranted. All chest roentgenograms were reviewed independently by at least two experienced radiologists.

Statistical Analysis

Pearson's chi-square test of the independence of two variables was used to test the significance of the interrelationship between various clinical parameters and roentgenographic findings. Data analysis was performed using the Clinical Study Unit computing facilities of the New England Medical Center.

RESULTS

Patient Characteristics

Fifty-four patients (37 men and 17 women) were treated with IL-2 with or without LAK cells. Thirty-one patients had melanoma, 15 had renal cell carcinoma, four had colon carcinoma, two had lymphoma, and one each had prostate carcinoma or sarcoma. The mean patient age was 47 years (range 22 to 66); 16 patients had received prior systemic therapy (seven chemotherapy, six hormonal, three immunotherapy), and seven had received prior radiotherapy. Twenty-seven patients had chest roentgenogram документed pulmonary metastases prior to therapy. The mean FEV₁ was 3.3 L (range 1.98 to 5.34 L) and 19 patients had FEV₁ less than 3 L.

Treatment

Forty-three out of a potential 44 patients (protocols 1a, 1b, 3 and 4) received autologous LAK cells (mean 8.3×10⁹, range 2.2×10⁹ – 13.2×10⁹), and 50 patients overall completed both scheduled courses of treatment. One patient did not receive LAK cells or further IL-2 because of respiratory complications. Three additional patients did not complete their second IL-2 course because of surgical intervention or death. A four-week follow-up chest x-ray film was obtained in 52 of the 54 patients.

Chest Roentgenographic Abnormalities

Chest roentgenographic abnormalities developed in 39 of 54 patients (72 percent) receiving IL-2 therapy. Abnormalities were classified as (1) pleural effusions; (2) a diffuse bilateral interstitial and/or alveolar pattern, pulmonary edema; or (3) infiltrates involving only one lobe or portion of a lung, "focal infiltrates." Concurrent abnormalities were frequent. Twenty-eight of 54 patients (52 percent) developed pleural effusions; 22 patients (41 percent) developed pulmonary edema, and 12 patients (22 percent) had focal infiltrates.

A minority of the roentgenograms, particularly...
in 30 of 39 patients (77 percent) by four weeks post therapy. The nine patients' roentgenograms that remained abnormal all showed small residual pleural effusions. Eight of 28 patients (29 percent) who received IL-2 solely by bolus intravenous injection (protocols 1a, 1b, or 2) had persistent pleural effusions, while only 1 of 24 patients (4 percent) who received a regimen involving the continuous infusion of IL-2 (protocols 3 or 4) had persistent abnormalities (p = 0.03).

Patients were analyzed as a function of their IL-2 treatment regimen, presence of pulmonary metastases, previous therapy, pretreatment pulmonary function (FEV₁), number of LAK cells received, and therapy-related percentage of weight gain, bacteremia, or pulmonary toxicity. Table 1 reports the incidence of different roentgenographic abnormalities, as well as the overall roentgenographic complication rate for each subgroup. A statistically significant increase in the overall rate of roentgenographic abnormalities was noted for patients receiving IL-2 solely by bolus intravenous injection (protocols 1a, 1b and 2) 25 of 30 (83 percent) vs those receiving continuous infusion or combination IL-2 (protocol 3 and 4) 14 of 24 (58 percent) (p = 0.04) as well as for patients with a pretreatment FEV₁ of less than 3 L, 17 of 19 (89 percent) vs those with a pretreatment FEV₁ of greater than 3 L, 22 of 35 (63 percent) (p = 0.04). The relationship between roentgenographic abnormalities in patients with treatment related bacteremia 11 of 12 (92 percent) vs those without such bacteremias 28 of 42 (67 percent) approached significance (p = 0.09). The remaining comparisons showed no statistically significant relationship with roentgenographic abnormalities. Although roentgenographic abnormalities were more frequent in the bolus IL-2 with LAK cell regimen (protocols 1a and 1b) 18 of 20 (90 percent) relative to the IL-2 alone regimen (protocol 2) 7 of 10 (70 percent),

![Figure 2](image1.jpg)

**Figure 2.** Twenty-two-year-old woman with melanoma who developed an isolated left pleural effusion during therapy.

toward the end of each treatment course, was performed with the patient supine, making the assessment of pleural effusions difficult and leading to a probable, slight underestimation of their prevalence. An example of a typical isolated pleural effusion is shown in Figure 2. The roentgenographic appearance of the focal infiltrates was nonspecific. These patients typically did not manifest clinical signs of infection, and therefore, these roentgenographic findings were felt to represent either a focal form of lung edema or focal atelectasis. A typical focal infiltrate is shown in Figure 3. The pattern of appearance of the IL-2 associated pulmonary edema was also nonspecific. Typically, there was diffuse bilateral airspace disease involving predominantly the lung bases (Fig 4). Although many examinations during therapy were performed using portable supine technique, making it difficult to assess cardiac size relative to baseline, there was no evidence of significant cardiomegaly.

The chest roentgenographic findings had resolved

![Figure 3](image2.jpg)

**Figure 3.** Sixty-two-year-old man with metastatic renal cell cancer who developed a left lower lobe (focal) infiltrate during therapy.

![Figure 4](image3.jpg)

**Figure 4.** Fifty-year-old man with melanoma who developed clinical and roentgenographic evidence of pulmonary edema during the first week of IL-2 therapy. Chest roentgenogram returned to normal after therapy.
Table 1—Relationships Between Clinical Characteristics and Roentgenographic Findings

<table>
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<th>Clinical characteristic</th>
<th>No.</th>
<th>Pleural Effusions, No. (%)</th>
<th>Pulmonary Edema, No. (%)</th>
<th>Focal Infiltrate, No. (%)</th>
<th>Any Abnorm., No. (%)</th>
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<td>13 (68)†</td>
<td>4 (21)</td>
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<td>&gt;3 L</td>
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<td>8 (23)</td>
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<td>7 (58)</td>
<td>7 (58)</td>
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<td>11 (92)‡</td>
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<tr>
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<td>8 (42)</td>
<td>6 (32)</td>
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<tr>
<td>10-15</td>
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<td>5 (33)‡</td>
<td>6 (40)</td>
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<tr>
<td>&gt;15</td>
<td>12</td>
<td>9 (75)‡</td>
<td>5 (42)</td>
<td>2 (17)</td>
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*See Figure 1.
†p = <0.05.
‡p = <0.10.

This difference was not statistically significant (p = 0.17).

There was no significant relationship between roentgenographic abnormalities and the degree of systemic capillary leak as measured by percentage of weight gain during treatment. This was particularly true for pulmonary edema which developed in 38 to 42 percent of patients irrespective of percentage of weight gain. However, patients who gained greater than 15 percent of their baseline weight during therapy were slightly more likely to have pleural effusions during treatment 9 of 12 (75 percent) and persistent effusions at four weeks following therapy 4 of 12 (33 percent) than those who gained less than 15 percent of their baseline weight 19 of 42 (45 percent) (p = 0.07) and 5 of 42 (12 percent) (p = 0.08), respectively.

Nineteen patients had significant pulmonary toxicity defined as dyspnea at rest (grade 3, n = 15) or requiring intubation and assisted ventilation (grade 4, n = 4). Only roentgenographic evidence of pulmonary edema appeared to relate significantly to clinical pulmonary toxicity. Fifteen of 19 (79 percent) patients who experienced grade 3 or 4 pulmonary toxicity exhibited pulmonary edema on their chest roentgenograms as compared with only 7 of 35 (20 percent) patients without significant pulmonary toxicity (p = 0.0001). Pulmonary edema appeared significantly more often in patients with pretreatment FEV<sub>i</sub> of less than 3 L, 13 of 19 (68 percent) than those with an FEV<sub>i</sub> of greater than 3 L, 9 of 35 (26 percent) (p = 0.002), and possibly more frequently in patients with prior chemotherapy, five of seven (71 percent), vs those without prior chemotherapy, 17 of 47 (35 percent) (p = 0.08).

Of the 39 patients whose course was complicated by roentgenographic abnormalities, 26 (67 percent)
developed these during the first week of IL-2 administration. Roentgenographic abnormalities during the first week of therapy with five-day bolus IL-2 regimens (protocols 1a, 1b, and 2) were particularly frequent, 20 of 30 (66 percent) relative to either the three-day bolus regimen (protocol 3) 5 of 17 (29 percent) or the continuous infusion regimen (protocol 4) one of seven (14 percent). Patients receiving greater than 10^{11} LAK cells had somewhat fewer x-ray findings during the first week, three of nine (33 percent), than those receiving less than 10^{11} LAK cells, 16 of 29 (55 percent) (p = 0.25), but showed no significant difference over the entire course of treatment, 25 of 32 (75 percent) vs 8 of 11 (73 percent). Thirty-three of 43 patients (77 percent) who received LAK cells developed abnormalities, and in ten patients, these abnormalities developed only after LAK cell administration. In two instances, chest roentgenograms performed within hours after the first LAK cell infusion revealed the rapid onset of bilateral perihilar infiltrates which corresponded with clinical signs of respiratory distress.

**DISCUSSION**

High-dose IL-2 therapy with or without LAK cells produced roentgenographic evidence of pulmonary toxicity in approximately 75 percent of patients. The roentgenographic patterns were nonspecific and included bilateral perihilar alveolar or interstitial infiltrates (pulmonary edema), focal infiltrates, and isolated pleural effusions. The pattern and frequency of chest roentgenogram abnormalities in our evaluation were similar to previous reports. However, we were able to correlate these x-ray findings with a variety of pretreatment and treatment-related clinical characteristics, thereby providing a clearer picture of potential risk factors and a better understanding of the role of chest roentgenograms in managing IL-2-associated pulmonary toxicity.

Pleural effusions were the most frequent abnormalities and were the slowest to resolve, persisting in 17 percent of patients four weeks following therapy. Diffuse pulmonary edema or focal infiltrates developed in 41 percent or 22 percent of patients, respectively, and resolved completely by four weeks after treatment in all patients. Pulmonary edema was more likely to be associated with significant respiratory difficulty and was more likely in patients with pretreatment FEV\(_1\) less than 3.0 L or who had received prior chemotherapy, while pleural effusions and focal infiltrates were of little clinical significance and did not correlate with pretreatment FEV\(_1\) or prior therapy.

Although most patients with chest roentgenograms showing pulmonary edema experienced pulmonary symptoms, 20 percent did not, suggesting that chest roentgenogram findings might be a useful early predictor of impending clinical pulmonary toxicity. Conversely, 4 of 19 patients with severe clinical pulmonary toxicity exhibited no roentgenographic evidence of pulmonary edema, suggesting that alternative mechanisms for pulmonary symptoms may occasionally be operative, (*eg*, respiratory compensation for a profound metabolic acidosis). Therefore, chest roentgenograms along with physical examination and arterial blood gas determinations, were frequently useful in distinguishing the cause of pulmonary symptoms.

Roentgenographic abnormalities occurred more frequently in patients with marginal pretreatment pulmonary functional reserve (FEV\(_1\),<3.0 L), those receiving IL-2 solely by intravenous bolus injection, and in patients who developed bacteremia during therapy. The increased frequency of roentgenographic abnormalities both during and following treatment (residual pleural effusions) in patients receiving intravenous bolus IL-2 (protocols 1 and 2) relative to continuous infusion IL-2 (protocols 3 and 4) is consistent with prior reports and perhaps reflects the greater intensity of the bolus treatment approach. There appeared to be no relationship between any of these chest roentgenographic patterns and the presence of pulmonary metastases or the quantity of LAK cells administered. Patients with the greatest percentage of weight gain were more likely to develop and have residual pleural effusions; yet, as had been noted by Saxon et al, there was no relationship between percentage of weight gain during treatment and the development of any other roentgenographic abnormality.

IL-2 therapy is associated with a systemic capillary leak syndrome which is believed to be responsible for the frequently observed hypotension, fluid retention, and renal insufficiency. Although several mechanisms have been postulated, the etiology of the IL-2-associated capillary leak syndrome remains unclear. IL-2 is known to induce the synthesis of several secondary cytokines, many of which are capable of activating endothelial cells. For example, tumor necrosis factor, IL-1, and IFN-gamma induce the expression of the leukocyte adhesion molecules’ intercellular adhesion molecule-1 (ICAN-1) and endothelial leukocyte adhesion molecule (ELAM) on the EC surface. These molecules facilitate the binding of leukocytes to the vascular lining which, in turn, may lead to EC damage and increased vascular permeability. Enhanced adhesion molecule expression is normally confined to sites of inflammation; however, skin biopsy samples from patients undergoing treatment with IL-2 have demonstrated EC expression of ICAM-1 and ELAM throughout the microcirculation. In addition, Aronson et al have shown that EC are readily lysed *in vitro* by IL-2-activated peripheral blood mononuclear cells (LAK cells) suggesting cell-mediated injury of the EC as another mechanism responsible for the
systemic capillary leak. However, the inability to correlate the majority of chest roentgenographic abnormalities observed in these patients with the degree of systemic capillary leak, as measured by treatment-related weight gain, suggests that processes other than generalized capillary leak may also be involved.

Although no relationship between the number of LAK cells administered and the overall frequency of roentgenographic abnormalities could be established, several lines of indirect evidence suggest that LAK cells may have contributed to the pulmonary toxicity. Ten patients developed roentgenographic abnormalities only after LAK cell therapy, and two patients developed rapid onset of severe dyspnea and roentgenographic findings of diffuse pulmonary edema within hours of receiving their first infusion of LAK cells. Although not statistically significant, the overall incidence of roentgenographic abnormalities was greater in patients who received intravenous bolus IL-2 with LAK cells than those who received intravenous bolus IL-2 alone. Furthermore, patients who generated and received larger numbers of LAK cells (>10^4) had fewer roentgenographic abnormalities during the first week of IL-2 administration, but a similar overall rate suggesting that the large number of LAK cells may have contributed to the roentgenographic abnormalities seen in these patients.

Despite the reports of cardiac dysfunction in patients undergoing IL-2 therapy,^{12,23} the apparent absence of cardiomegaly on chest x-ray films, and the repeatedly normal central venous pressure determinations (data not shown) make a cardiogenic cause for pulmonary edema unlikely. Several published reports support this conclusion. Gaylor et al^{20} found that patients receiving IL-2/LAK cell therapy developed significant falls in systemic vascular resistance accompanied by a slight fall in left ventricular ejection fraction, but compensatory rises in heart rate and cardiac index were sufficient to maintain their pulmonary capillary wedge pressure in the normal range. Lee et al,^{11} using radionuclide angiography, found that LVEF decreased only from 58 to 52 percent during IL-2/LAK cell treatment while the PCWP remained stable. Finally, Mann et al^{14} also showed minimal change in CVP readings despite the development of roentgenographic evidence of interstitial and alveolar edema in 53 and 21 percent of patients, respectively. However, since it was difficult to accurately assess cardiac size and function during therapy, it is possible, as was suggested by Davis et al,^{15} that cardiac dysfunction may have contributed to the pulmonary edema in some IL-2 recipients.

The hemodynamic effects of IL-2 therapy have been likened to those of sepsis. The diffuse, noncardiogenic pulmonary edema seen with IL-2 therapy is reminiscent of the adult respiratory distress syndrome, which can also be seen in the setting of sepsis. The pathogenesis of ARDS has been studied extensively and is felt to be multifactorial. Activated complement has been implicated in the genesis of ARDS complicating sepsis and trauma.^{25-28} Activated complement has also been detected in the circulation of IL-2 recipients,^{29} suggesting that it may be causally related to the noncardiogenic pulmonary edema that develops in some patients treated with IL-2. Adult RDS often progresses to involve all elements of the lung with resultant permanent architectural derangement and fibrosis. Although irreversible pulmonary changes are usually not seen in IL-2 recipients, the IL-2-related toxicity may parallel the earlier stages of ARDS.

These observations suggest that pulmonary complications from IL-2 therapy may be related to more than just the generalized capillary leak syndrome. Regardless of the mechanism, the extravasation of fluid into the pleural space and the alveoli is probably aggravated by the profound hypoalbuminemia that routinely develops during IL-2 treatment.^{5,6} An understanding of the risk factors, roentgenographic appearance, and clinical significance of the chest radiographic abnormalities associated with IL-2 therapy may allow for the safer administration of this promising, but toxic therapy.

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