Interleukin-2 Administration Causes Reversible Hemodynamic Changes and Left Ventricular Dysfunction Similar to Those Seen in Septic Shock*

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Interleukin-2, a lymphocyte product, has well demonstrated antitumor activity in humans. Early clinical studies showed hemodynamic alterations in patients receiving the drug as antitumor immunotherapy. We serially assessed interleukin-2-associated hemodynamic parameters and left ventricular ejection fractions in five patients with neoplastic diseases unresponsive to conventional therapies. By day 4 of therapy, compared with baseline (preinterleukin-2), all patients developed tachycardia (p<0.01), decreased mean arterial blood pressure (p<0.05), increased cardiac index (p<0.05), and decreased systemic vascular resistance (p<0.01). In addition, left ventricular ejection fraction fell from 58.0±4.7 to 36.4±4.0 percent (0.05<p<0.10), which was associated with a trend toward left ventricular dilatation manifested by an increase in left ventricular end-diastolic volume index. Transient renal dysfunction was noted in all five patients, and one developed transient respiratory failure; both types of organ dysfunction recovered to baseline values after cessation of immunotherapy. Thus, interleukin-2 induces multiple reversible cardiovascular abnormalities that are similar to the hemodynamic manifestations of human septic shock. (Chest 1998; 104:730-54)

Interleukin-2 is a glycoprotein produced by human T-lymphocytes that have been activated by mitogens or antigens. Interleukin-2 has been shown to mediate numerous in vivo immune phenomena, including enhancement of natural killer cell cytotoxicity and augmentation of alloantigen responsiveness. Incubation of resting lymphocytes in interleukin-2 results in the generation of lymphokine-activated killer cells which can lyse fresh tumor cells. Recombinant interleukin-2 can be purified and produced in large quantities with the same biologic activity as natural interleukin-2, enabling its use in human clinical trials. Interleukin-2, alone and with lymphokine-activated killer cells, has been shown to have substantial antitumor activity in certain animal tumor models. Recently, human trials have shown that administration of interleukin-2, either alone or with lymphokine-activated killer cells, can mediate the regression of metastatic cancer caused by a variety of tumor types.

Some of the initial human studies revealed that interleukin-2 administration was temporally associated with reversible hemodynamic alterations including tachycardia and hypotension. The purpose of this limited study was to assess formally the hemodynamic effects of interleukin-2, using continuous hemodynamic monitoring and determinations of left ventricular ejection fractions from radionuclide cardiac angiography, in patients receiving the agent as antineoplastic immunotherapy.

**Material and Methods**

**Patients**

Patients with tumors unresponsive to conventional therapy were admitted to the medical intensive care unit at the National Institutes of Health before the administration of interleukin-2, with or without the addition of lymphokine-activated killer (LAK) cells. All patients had consented to therapy with interleukin-2, and additional informed consent was obtained from each patient before any invasive hemodynamic monitoring.

**Hemodynamic Monitoring**

Heart rate (HR) was monitored using Hewlett-Packard ECG equipment. Arterial blood pressure was monitored by an indwelling radial or femoral artery catheter. A pulmonary artery (Swan-Ganz) catheter was positioned in the pulmonary artery outflow tract of each patient, using fluoroscopic guidance, and was used for measurements of central venous pressure (CVP) and pulmonary artery wedge pressure (PAWP). The measurement of PAWP was made using our standard protocol technique with the patient supine and the zero reference point adjusted to 5 cm posterior to the sternum in the midaxillary line. All PAWP measurements were determined from paper tracings on a Hewlett-Packard strip chart recorder at end-expiration and after the characteristic dampening of the pulmonary artery waveform pattern. All peripheral arterial and pul-

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monary arterial pressure measurements were standardized to mercury.

The pulmonary artery catheters were also used for determinations of cardiac output by the thermodilution technique. A series of three to five consecutive determinations of cardiac output using 10 ml of 5 percent dextrose in water was performed. The mean of either three values that varied by less than 10 percent or of the three closest determinations (of five) after elimination of the high and low values was the CO recorded at that time point. All CO values were standardized to cardiac index (CI) based on patient weight using the standard formula: CI = CO/BSA (BSA = body surface area).

Using standard formulas, left ventricular stroke work index (LVSWI) and systemic vascular resistance (SVR) were also determined at the time of each CO/CI determination.

Radionuclide cineangiography studies were performed in these patients during their courses of interleukin-2 immunotherapy. Patients received a single injection of approximately 20 mCi of 99mTc to label the patients' erythrocytes in vivo, and left ventricular ejection fractions were calculated using standard nuclear medicine techniques. These radionuclide studies were performed simultaneously with the hemodynamic determinations.

All patients had constant monitoring of heart rate and mean arterial blood pressure. Hemodynamic determinations, ie, CI, PAWP, LVSWI, and SVR, were performed at least three times a day in each patient. Radionuclide studies were performed as a baseline before the administration of interleukin-2 and at days 3 to 5 of interleukin-2 administration. When possible, recovery LVEF studies after termination of interleukin-2 therapy were performed.

Infusion of Recombinant Interleukin-2 and Lymphokine-activated Killer Cells

Therapy consisted of IV interleukin-2 and LAK cells, IV interleukin-2 alone, or intraperitoneal interleukin-2. Interleukin-2, in doses of 100,000 units/kg, was administered every eight hours for at least four days in every patient. The recombinant interleukin-2 was diluted in 50 ml of normal saline and albumin and administered over a 15-minute period. Lymphocytes were obtained via repeated leukophereses, as previously described, for generation of activated killer cells. These cells were placed in suspension and administered on days 1, 2, and 4.

Urinary output was monitored closely, and renal function was assessed with three times daily serum creatinine and BUN determinations. Respiratory status was assessed subjectively (dyspnea) and objectively with serial arterial blood gas determinations and chest roentgenograms. Therapy with interleukin-2 was terminated if any of the following clinical situations occurred: progressive hypotension despite fluid or vasopressor administration or progressive organ dysfunction such as respiratory distress with increasing 

RESULTS

In this study, five patients received high-dose (100,000 units/kg) interleukin-2, and four of these five patients also received LAK cells as antineoplastic immunotherapy for a duration of at least four days. Clinical data are summarized in Table 1. The underlying diseases were renal cell carcinoma (2), malignant melanoma (1), rhabdomyosarcoma (1), and widespread Kaposi's sarcoma due to the acquired immunodeficiency syndrome (1). None of these patients had received doxorubicin or other anthracycline derivatives as part of their prior chemotherapeutic regimens.

The acute clinical effects of the immunotherapy regimen were similar in all five patients. All patients developed fever and rigors, with temperature greater than 39°C within 24 hours of the initiation of interleukin-2. Despite the fever and rigors, all of these patients had two or more daily negative blood cultures during the courses of interleukin-2 administration.

Statistical Methods

Statistical analysis of the mean ± SEM changes in all hemodynamic parameters and changes in renal function was performed using a paired sample t test comparing the differences between baseline (day 0) and final (day 4) data. A p value of less than 0.05 was considered to demonstrate statistical significance.

Table 1—Clinical Characteristics of Patients Receiving Interleukin-2 Immunotherapy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, yr</th>
<th>Sex</th>
<th>Underlying Disease</th>
<th>Interleukin-2 Site of Administration</th>
<th>Lymphokine Activated Killer Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24</td>
<td>M</td>
<td>Malignant melanoma</td>
<td>Intraperitoneal</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>M</td>
<td>Renal cell carcinoma</td>
<td>IV</td>
<td>Yes</td>
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<tr>
<td>3</td>
<td>54</td>
<td>F</td>
<td>Renal cell carcinoma</td>
<td>IV</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>33</td>
<td>M</td>
<td>Rhabdomyosarcoma</td>
<td>IV</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>M</td>
<td>Acquired immunodeficiency syndrome/Kaposi's sarcoma</td>
<td>IV</td>
<td>Yes</td>
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</table>
hours of interleukin-2 administration. The mean increase in heart rate of 54.4 ± 8.5 beats/min between day 0 and day 4 was statistically significant (p<0.01). Mean arterial blood pressure fell within 24 hours in all five patients, and all except patient 5 required vasopressor support of up to 20 μg/kg/min of dopamine to maintain their blood pressures. The decrease in mean arterial blood pressure of 26.8 ± 8.4 mm Hg between day 0 and day 4 was statistically significant (p<0.05). All patients also experienced a statistically significant (p<0.01) fall in systemic vascular resistance of 443.6 ± 69.1 dynes·sec/cm² between day 0 and day 4.

Concomitantly, serial cardiac indices in each patient rose. From day 0 to day 4, the increase of 1.60 ± 0.56 L/min/m² was statistically significant (p<0.05). Left ventricular stroke work index decreased from day 0 to day 4; the decrement of 25.3 ± 9.5 g/min/m² approached, but did not achieve, statistical significance with 0.05<p<0.10.

The hemodynamic data listed in Tables 2 and 3 indicate the effects of interleukin-2 during its administration. After discontinuation of interleukin-2 therapy, all patients had a recovery of these hemodynamic parameters to baseline values. The time for return to baseline varied in each individual, but occurred within 48 hours in all except patient 4, who fully recovered 14 days after discontinuation of interleukin-2.

Figure 1 presents the changes in left ventricular ejection fractions, as measured by radionuclide cineangiography, and changes in the simultaneously determined left ventricular end-diastolic volume indices. Left ventricular ejection fraction data were available and interpretable in four of the five patients. Baseline ejection fractions were normal in all patients, with a mean of 58.0 ± 4.7 percent. By days 3 to 5 of interleukin-2 administration, all four patients had decrements in left ventricular ejection fraction to a mean of 36.4 ± 4.0 percent. This difference in ejection fraction approached statistical significance, p<0.10.

End diastolic volume index data were available in 3 of the 4 patients who had interpretable ejection fractions. All of these patients demonstrated an increase in their end-diastolic volume, indicative of left ventricular dilatation, which was associated with the depression in the ejection fraction.

Other Clinical Data

All patients developed oliguria, despite maintenance of an adequate intravascular volume, eg, pulmonary artery wedge pressure greater than 10 mm Hg. All patients required diuretic therapy to maintain urinary output; however, serum creatinine levels still rose from 1.0 ± 0.03 mg/dl at day 0 to 2.0 ± 0.28 at day 4 (p<0.02). After cessation of interleukin-2, all patients had a return of serum creatinine to normal.

One patient (no. 4) developed transient respiratory failure characterized by diffuse alveolar and interstitial infiltrates on chest roentgenogram and hypoxemia which required endotracheal intubation and support with mechanical ventilation and positive end-expiratory pressure (PEEP). There was no evidence for an

<table>
<thead>
<tr>
<th>Day</th>
<th>Heart Rate, beats/min</th>
<th>Mean Arterial Pressure, mm Hg</th>
<th>Systemic Vascular Resistance, dynes/cm²</th>
<th>Cardiac Index, L/min/m²</th>
<th>Left Ventricular Stroke Work Index, g/min/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>84.0 ± 3.5</td>
<td>90.8 ± 7.4</td>
<td>873.4 ± 91.8</td>
<td>4.27 ± 0.49</td>
<td>57.0 ± 8.1</td>
</tr>
<tr>
<td>1</td>
<td>106.4 ± 11.2</td>
<td>76.8 ± 7.6</td>
<td>551.6 ± 100.4</td>
<td>5.71 ± 0.82</td>
<td>52.3 ± 8.1</td>
</tr>
<tr>
<td>2</td>
<td>115.6 ± 10.5</td>
<td>68.2 ± 3.0</td>
<td>565.2 ± 81.7</td>
<td>5.49 ± 0.83</td>
<td>38.9 ± 6.6</td>
</tr>
<tr>
<td>3</td>
<td>131.2 ± 16.1</td>
<td>67.6 ± 4.1</td>
<td>459.8 ± 71.5</td>
<td>6.21 ± 0.94</td>
<td>46.6 ± 11.5</td>
</tr>
<tr>
<td>4</td>
<td>138.4 ± 6.9</td>
<td>64.0 ± 4.4</td>
<td>429.8 ± 63.9</td>
<td>5.88 ± 0.66</td>
<td>31.7 ± 3.8</td>
</tr>
</tbody>
</table>

*p<0.05 compared to day 0, using paired sample t test.
†p<0.01 compared to day 0, using paired sample t test.

Table 3—Individual Patient Hemodynamic Parameters on Day 0 and Day 4 of Interleukin-2 Administration
infectious pneumonia, with multiple negative blood and sputum cultures, which demonstrated only normal flora. This patient received aggressive volume replacement in addition to vasopressor therapy because of hypotension. By day 4 of interleukin-2 therapy, this patient had a net weight gain of 22 kg. Despite the aggressive fluid resuscitation, the patient's pulmonary artery wedge pressure remained less than 18 mm Hg. Interleukin-2 therapy was terminated at the time the patient required intubation. This patient's pulmonary and hemodynamic parameters were most consistent with a noncardiogenic decompensation such as the adult respiratory distress syndrome. His pulmonary function eventually recovered to its baseline status by 14 days after discontinuation of interleukin-2 therapy.

**DISCUSSION**

Interleukin-2 administration was associated with a hemodynamic pattern that is similar to the hemodynamic changes seen in septic shock. These alterations, which occurred within 24 hours of interleukin-2 administration, included profound tachycardia, decreased mean arterial blood pressure, increased cardiac index, decreased systemic vascular resistance, and decreased left ventricular stroke work index. All of these hemodynamic changes have been well described in human septic shock. The alterations in blood pressure and systemic vascular resistance required vasopressor administration in four of the five patients studied. There was neither evidence of bacteremia in the patients nor of endotoxin in the interleukin-2 administered. Therefore, although the hemodynamic profile seemed similar to sepsis, an infectious etiology could not be documented, and one must conclude that the cardiovascular pattern resulted from direct or indirect effects of interleukin-2.

Primary myocardial dysfunction was also demonstrated in these patients during interleukin-2 administration. The depressed left ventricular ejection fraction associated with left ventricular dilatation seemed to peak at days 3 to 5 of interleukin-2 administration. This depression of left ventricular ejection fraction has been demonstrated to be present and reversible in patients with sepsis and septic shock and in canine models of human septic shock. Data have recently been generated which demonstrated similar falls in left ventricular ejection fraction in a somewhat larger group of patients who received interleukin-2. Their depressed ejection fractions were most dramatic by day 5 of interleukin-2 therapy and were reversible, with ejection fractions returning to baseline values after interleukin-2 therapy had been discontinued. That the depression of ejection fraction was reversible seems to indicate a causal relationship between the fall in ejection fraction and either interleukin-2 therapy directly or perhaps another mediator generated or released by this immunotherapeutic agent.

Transient renal dysfunction, manifested by oliguria and a rise in serum creatinine level, was observed in all of our patients. These alterations in renal function have been well described as effects of interleukin-2 in a much larger group of patients. Although only seen in one patient in our study population, transient pulmonary dysfunction, manifested by hypoxemia and bilateral pulmonary infiltrates, may also complicate the administration of interleukin-2. This renal and pulmonary dysfunction may represent end organ damage analogous to that seen in sepsis. Such organ damage may be speculated to be due to either direct endothelial damage by interleukin-2 or to alterations in organ blood flow and perfusion, both of which are mechanisms postulated to lead to organ failure in sepsis.

As in sepsis, the mechanisms of these hemodynamic and cardiovascular alterations are not entirely known. One may speculate that they are direct manifestations of interleukin-2, or they may be due to the ability of interleukin-2 to activate other mediators such as...
complement, kinins, or prostaglandins. A more thorough understanding of the pathogenesis of these interleukin-2-associated hemodynamic aberrations may lead to a better comprehension of the similar alterations seen in sepsis.

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REFERENCES