Systemic and Hemodynamic Effects of Recombinant Tumor Necrosis Factor Alpha in Isolation Perfusion of the Limbs*

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Objective: To describe the systemic effects of high-dose recombinant tumor necrosis factor alpha (rTNF-α), recombinant interferon gamma (rIFN-γ), and melphalan administered through hyperthermic isolation perfusion of the limbs (IPL) in patients with melanoma and malignant soft-tissue tumors.

Design: The clinical, hemodynamic, and biologic parameters were recorded after IPL during the postoperative period.

Setting: Surgical intensive care service of a 1,000-bed tertiary university medical center.

Patients: Nineteen patients referred to a pluridisciplinary Center for Oncology after relapse of regionally advanced melanoma or soft-tissue tumors, included in a phase 2 therapeutic study.

Results: Major systemic and hemodynamic changes were observed after IPL in all patients. Ninety-four percent (17/18) of the evaluable patients presented a shock unresponsive to fluid challenge, requiring the continuous perfusion of vasopressors, inotropic agents, or both. Analysis of hemodynamic data showed two distinctive patterns: a pure distributive shock in nine patients, requiring norepinephrine, and a mixed distributive and cardiogenic shock in eight patients requiring vasopressor and inotropic agents. The oxygen parameters were characterized by an increase in both the delivery and the uptake of oxygen, with a prolonged reduced oxygen extraction ratio for most patients. The other observed effects were as follows: transient bilateral or mixed pulmonary infiltrates in all patients; some hemolologic disturbances in 83% of patients; infection requiring a modification of the antibiotic prophylaxis in 61% of patients; and some liver toxic reactions in 50% of patients. Very high systemic TNF-α serum bioactivity was found in 12 patients for whom serum samples were available, indicating an early and important rTNF-α leakage from the IPL. No correlations could be found between the levels of TNF-α and the observed systemic effects. Despite the severity of the hemodynamic disturbance, no patient died.

Conclusion: Major systemic effects, consisting mainly in cardiovascular, respiratory, and hemolologic disturbances, were observed in patients after IPL with high-dose of rTNF-α. The likely explanation for these observations is an early rTNF-α leakage related to inadequate IPL technique. These data show that the iatrogenic administration of high circulating TNF levels lead to a “septic shock-like” syndrome without resulting in lethal organ dysfunction. (Chest 1995; 107:1074-82)

Cytokines are polypeptides produced by cells of the immune system and other cells exposed to various stimuli (microorganisms, endotoxin, or mechanical trauma). They are primarily devoted to transmitting information to other cells. In addition, they are responsible for systemic effects such as induction of fever and stimulation of acute-phase proteins produced by the liver. Some have anti-inflammatory effects (interferon [IFN]; interleukin-6 [IL-6]), but others are proinflammatory agents, particularly tumor necrosis factor alpha (TNF-α) and interleukin-1 (IL-1). Cytokines appear to be major mediators of the immune response and play a mandatory role in type B and T cellular response. Moreover, large amounts of TNF-α and IL-1 produced in response to microbial products (endotoxin particu-
larly) may become central mediators of the systemic reactions such as fever, inflammation, tissue lesions, metabolic dysfunctions, sepsis, septic shock, and multiple organ failure (MOF).  

Tumor necrosis factor alpha is a 17-kd polypeptide mainly produced by monocytes and macrophages in response to microorganism products (endotoxin, teichoic acid, exotoxin, and other). It is an important mediator of the cardiovascular dysfunction characteristic of sepsis and septic shock.  

In patients with meningococcemia or septic shock, the serum levels of TNF-α have been shown to correlate with survival. An interesting property of TNF-α is the efficient hemorrhagic and coagulative necrosis of transplanted tumors that it produces in animals. Phase 1 trials of treatment with recombinant TNF-α (rTNF-α) (intratumoral, subcutaneously, intramuscularly, or intravenously) have reported promising results in some patients with cancer, consisting of necrosis of the tumor. However, these studies found that severe systemic side effects limited the maximal tolerated dose at about 200 to 400 µg/m³. Combined with recombinant human interferon-gamma (rIFN-γ), which increases the number of TNF receptors on tumor cells, the administration of very high doses of both rTNF-α (3 to 4 mg) and melphalan (40 to 120 mg) in hyperthermic isolated limb perfusion (IPL) was recently shown to be active in the treatment of metastatic melanoma or soft-tissue sarcoma. The adverse effects associated with this triple-drug regimen were mild and mainly attributed to TNF-α. Despite extremely high amounts of bioactive TNF-α released in the circulation from the extravascular compartment after the end of the IPL, followed by a delayed release of high amounts of IL-6, no correlation could be found between TNF-α and the systemic effects observed.  

Such therapy was recently introduced in our institution and was associated with major side effects. The aim of this retrospective study is to report our experience on the systemic effects of rTNF-α released systemically after IPL.

**Material and Methods**

**Patient Selection**

All patients were referred to the Multidisciplinary Center for Oncology for relapse following conventional therapy for regionally advanced melanoma (stage III A and III AB) or sarcoma. The protocols were approved by the ethical committee of our institution (1,000-bed tertiary-university hospital). After extended work-up and oral informed consent, in accordance with the Swiss rules for medical research, the patients were all included in a phase 2 multicentric study. Patients with severely impaired cardiac function were excluded. Patients with melanoma were randomized to be treated by a double-drug-regimen (rTNF-α and melphalan) or by a triple-drug regimen (rTNF-α, rIFN-γ, melphalan) in hyperthermic IPL. Other malignant soft-tissue tumors were treated by the triple-drug regimen.

**IPL**

Isolation perfusion of the limb was performed under general anesthesia via the iliac, or femoral or subclavian vessels, using a standard technique. A membrane oxygenator (Variable Prime Cobe Membrane Lung Plus, Cobe Cardiovascular, Arvada, Colo) with silicone tubing was used. The system was primed with 1 U of red blood cells, 1 L of hydroxyethylstarch solution (Haes-steril 6%, Fresenius AG, Stans, Switzerland). The perfusate flow reached rapidly 0.7 to 1 L/min for the lower limb and 0.2 to 0.4 L/min for the arm. At the end of the IPL, a standard washout procedure was performed using 2 L of a crystalloid solution (Hartmann Ringer-lactate, Vifor, Geneva, Switzerland). Four thermistor probes were implanted in the subcutaneous tissues and into the muscles to monitor the tissue temperature, which ranged between 38°C and 40°C.

**Drugs**

Human recombinant TNF-α (0.2 mg per vial) and human recombinant IFN-γ (0.2 mg or 1.5X10⁶ U per vial) were provided by the manufacturer (Boehringer Ingelheim, Germany). Both were stored as a lyophilized powder that was aseptically reconstituted with 1 mL sterile saline solution. Prior to IPL, all patients received 1.5X10⁶ U IFN-γ per day subcutaneously for 2 days before surgery. For the patients assigned to receive the triple-drug regimen containing rIFN-γ perfusion, 0.2 mg of the drug was injected in the arterial line at the beginning of the IPL. According to previous procedure, 4 mg of rTNF-α for a leg or 2 mg for an arm was infused at the arterial line of the IPL when tissue temperature reached 38°C. The melphalan dose (Alkeran, Burroughs Wellcome, London, UK) was calculated according to the “liter-volume” method to give a plasma concentration at equilibrium of 40 µg/mL, and 33 to 100 mg was administered 30 min later. Indomethacin was administered intravenously (IV) (50 mg over 4 h, followed by 200 mg over the next 20 h) to decrease systemic adverse manifestations. Just before cannulation of the limb vessels, 200 IU/kg heparin was given IV and a continuous infusion of dopamine (3 to 5 µg/kg/min) was started, which lasted until the procedure was ended and the patient was transferred from the ICU. These treatments were then maintained until complete recovery and discharge from ICU. The whole perfusion lasted 90 min, and the limb was then washed with a hydroxyethylstarch solution (Haes-steril 6%, Fresenius AG, Stans, Switzerland). Antibiotic prophylaxis consisted of five doses of a first-generation cephalosporin.

**Type and Technique of Anesthesia and ICU Monitoring**

To provide stable hemodynamic parameters for a 6- to 10-h surgical operation, we chose an anesthesia technique similar to that used for cardiac surgery procedures. Induction and maintenance anesthesia consisted of lorpazepam or midazolam, fentanyl, and pancuronium. Due to the potential high risk of distributive shock, halogenate agents were not used. Arterial and pulmonary catheters were inserted in all patients after induction of anesthesia and the following parameters were monitored until the end of ICU stay: continuous five-lead ECG; hourly urine output; pulse-oximetry (SpO₂); systolic (SABP), mean (MABP), and diastolic (DABP) arterial blood pressure, central venous pressure (CVP), mean pulmonary artery pressure (MPAP), and pulmonary capillary wedge pressure (PCWP). Cardiac output (CO) was measured by the thermodilution method in triplicate and pulmonary arterial blood oximetry (SaO₂) was determined by Co-oximetry.

**Definitions**

Shock was defined as hypotension with SBP ≤90 mm Hg despite adequate fluid resuscitation (or a sustained decrease in SBP ≥40 mm Hg rom baseline). The following patterns of shock
were considered: (1) distributive shock: a high cardiac index (CI, CO/body surface in m²) $\geq 4.5$ L/min/m² associated with low indexed systemic arterial resistances (SARi = MAP-CVP/CI × 80Xbody surface) $\leq 1,200$ dyne·s·cm⁻²/m² in patients requiring vasopressor therapy after a sufficient fluid challenge; (2) mixed shock: a normal or low CI $< 3.0$ L/min/m² associated with low SARi $\leq 1,200$ dyne·s·cm⁻²/m² in patients requiring a combination of vasopressor and inotropic agents after a sufficient fluid challenge. Oxygen transport parameters were defined as follows: oxygen delivery (DO₂ in mL/min×m²) as the product of CI and arterial content in O₂ (CaO₂ = 1.3×Hb×SaO₂×10); oxygen uptake (VO₂ in mL/min × m²) as the product of CI and the difference between arterial and venous O₂ contents (CaO₂ = 1.3×Hb×SvO₂×10). ARDS was defined as the presence of a low PaO₂ (O₂ inspired fraction ratio [PaO₂/FI O₂] <120) associated with bilateral pulmonary interstitial and mixed infiltrates in patients with normal or low PCWP (<15 mm Hg).

**Postoperative Management**

At the end of the operation, all patients were admitted to the surgical ICU, and they were mechanically ventilated until they recovered from anesthesia and were extubated. All the above-mentioned parameters were prospectively monitored. The CI and SvO₂ were determined at admission, then at 6, 12, 24, and 48 hours after the administration of rTNF-α or when indicated by the patient’s clinical condition. In all patients, the goal was to maintain CI over 4.5 L/min/m², DO₂ over 600 mL/min×m², and VO₂ over 170 mL/min×m².6,36,37

**Assessment of Tumor Response**

Tumor response was assessed using standardized criteria as in our previous study.28,29

**Measurement of TNF-α**

A highly sensitive mouse fibrosarcoma cell line, WEHI 164 clone 13 (provided by J. Tschopp, Institute of Biochemistry, Lausanne, Switzerland), was used to measure serum TNF-α levels, as originally described by Espevik and Nissen-Meyer.38 The limit of detection was <0.5 pg/mL.

**Data Analysis**

The changes in the various parameters throughout the study in the two groups were assessed using nonparametric tests (the Friedman and the Wilcoxon tests), using a software package (Statview, Brainpower, Calabasas, Calif). A p value of <0.05 was considered significant.

**RESULTS**

**Characteristics of Patients**

Nineteen patients were included in the study from February 1992 to March 1993. Their characteristics are listed in Table 1. Thirteen patients suffered from one (or more) associated illnesses that may worsen the systemic response to IPL, the hemodynamic response to IPL, or both, including nine patients with cardiopathies of various origin. The conditions of these patients were well stabilized and they were asymptomatic with adequate therapy. Isolation perfusion of the limb was performed via the iliac vessels in nine patients, the femoral in five, and the subclavian in four. One patient was treated a second time for a regional relapse after 8 months. All patients except one were treated with the triple-drug-regimen consisting of rTNF-α, rIFN-γ, and melphalan. The mean stay in the ICU was 98 h (range, 43 to 120 h).

**Tumor Response**

At hospital discharge, all patients were alive and presented a spectacular softening of the tumor. At 12 weeks, complete response was maintained in 68% of patients (13/19: melanoma 12; sarcoma 1) and partial response was present in 21% of patients (4/19: sarcoma 2; melanoma 1; squamous cell carcinoma 1). After a median follow-up of 21 months, 74% of patients were alive (three patients dead from metastatic melanoma and two from metastatic sarcoma). Forty percent of survivors were free of tumor (melanoma, 4/11; sarcoma 1/1; squamous cell carcinoma, 1/2) and a dissemination of the tumor occurred in 27% of patients with melanoma.

**Anesthesia**

Hypotension developed in all patients during anesthesia, at the end of IPL promptly after tourniquet removal, which responded to an aggressive fluid challenge alone in 12 of 19 (63%). Perioperative perfusions consisted in blood products (red blood cells: mean value 5.0; range, 0 to 25 U; fresh frozen plasma: mean 3; range, 0 to 10 U) and crystalloids/artificial colloids solutions (colloids: mean volume, 1,100 mL; range, 0 to 2,000 mL; crystalloids: mean, 4,100 mL; range, 2,500 to 8,000 mL). One patient required an emergency arterial thrombectomy a few hours after...
Table 2—Hemodynamic Patterns and Systemic Response, Mean (Range) After High-dose rTNF-a Administered Through IPL

<table>
<thead>
<tr>
<th>Type of Shock</th>
<th>Distributive (n=9)</th>
<th>Mixed (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>56.7 (36-68)</td>
<td>60.3 (40-79)</td>
</tr>
<tr>
<td>Previous cardiopathy</td>
<td>44% (4/9)</td>
<td>63% (5/8)</td>
</tr>
<tr>
<td>Fever &gt;38°C</td>
<td>89% (8/9)</td>
<td>63% (5/8)</td>
</tr>
<tr>
<td>Mean Temperature, °C</td>
<td>39.0</td>
<td>37.9</td>
</tr>
<tr>
<td>MABP,* mm Hg</td>
<td>56 (48-68)</td>
<td>56 (44-61)</td>
</tr>
<tr>
<td>CL* L/min/m²</td>
<td>5.5 (4.6-6.7)</td>
<td>2.4 (1.8-3.0)</td>
</tr>
<tr>
<td>SARI,* dyne·s·cm⁻⁵/m²</td>
<td>939 (604-1,116)</td>
<td>909 (790-1,150)</td>
</tr>
<tr>
<td>PaO₂/FI₂ ratio</td>
<td>239 (182-350)</td>
<td>209 (112-350)</td>
</tr>
<tr>
<td>Noradrenaline Maximal dosage, µg/kg/min</td>
<td>0.24 (0.08-0.43)</td>
<td>0.24 (0.05-0.5)</td>
</tr>
<tr>
<td>Duration of administration, h</td>
<td>44 (24-77)</td>
<td>47 (27-69)</td>
</tr>
<tr>
<td>Dobutamine Maximal dosage, µg/kg/min</td>
<td>—</td>
<td>6.9 (2.7-21)</td>
</tr>
<tr>
<td>Duration of administration, h</td>
<td>—</td>
<td>40 (13-70)</td>
</tr>
<tr>
<td>TNF-a: peak of serum bioactivity Mean, ng/mL</td>
<td>118.89</td>
<td>112.82</td>
</tr>
<tr>
<td>Range, ng/mL</td>
<td>1.12-365.44</td>
<td>21.3-326.75</td>
</tr>
</tbody>
</table>

*MABP=mean arterial blood pressure; SARI=systemic arterial resistances indexed.

### Mixed shock

#### Cardiac index (L/min/m²)

- *p < 0.05

#### Systemic arterial resistances indexed (dyne·sec/cm²/m²)

- *p < 0.05

#### Oxygen intake (ml/min/m²)

#### Norepinephrine (µg/kg/min)

#### Dobutamine (µg/kg/min)

### Distributive shock

#### Cardiac index (L/min/m²)

- *p < 0.05

#### Systemic arterial resistances indexed (dyne·sec/cm²/m²)

- *p < 0.05

#### Oxygen intake (ml/min/m²)

#### Norepinephrine (µg/kg/min)

#### Dobutamine (µg/kg/min)

**Figure 1.** Pattern of shock after IPL: distributive shock (n=9) or mixed shock (n=8). Mean value±SD, cardiac index, systemic arterial resistances indexed, oxygen intake at different times after IPL, p<0.05 vs baseline (time A). A=general anesthesia, before IPL; B=administration of TNF through IPL; C=1 h after TNF administration; D=3 h after TNF administration; E=8 h after TNF administration; F=1 day after TNF administration; G=2 days after TNF administration; and H=3 days after TNF administration.
Table 3—Systemic and Local Response After High-Dose rTNF-α Administered Through IPL*

<table>
<thead>
<tr>
<th>Factor</th>
<th>WHO Grade</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>4</td>
<td>19/19</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cells</td>
<td>4</td>
<td>3/19</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3/19</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1/19</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>7/19</td>
</tr>
<tr>
<td>Thrombocytes</td>
<td>4</td>
<td>2/19</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>8/19</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1/19</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>5/19</td>
</tr>
<tr>
<td>Blood chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGOT/SGPT</td>
<td>3</td>
<td>4/19</td>
</tr>
<tr>
<td>Serum bilirubin</td>
<td>3</td>
<td>3/19</td>
</tr>
<tr>
<td>Rhabdomyolysis (CK &gt;10 fold)</td>
<td>2</td>
<td>3/19</td>
</tr>
<tr>
<td>Perfused limb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial obstruction related</td>
<td>1</td>
<td>1/19</td>
</tr>
<tr>
<td>to high hyperthermia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Documented deep venous</td>
<td>1</td>
<td>1/19</td>
</tr>
<tr>
<td>thrombosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluid challenge during the</td>
<td></td>
<td></td>
</tr>
<tr>
<td>first 24 h after IPL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood, U</td>
<td>4.0 (2-12)</td>
<td>1/19</td>
</tr>
<tr>
<td>Frozen plasma, U</td>
<td>3.0 (0-9)</td>
<td>1/19</td>
</tr>
<tr>
<td>Colloids, mL</td>
<td>2,500 (2,000-3,500)</td>
<td>1/19</td>
</tr>
<tr>
<td>Cristalloids, mL</td>
<td>3,360 (2,200-6,300)</td>
<td>1/19</td>
</tr>
</tbody>
</table>

*CK=creatine kinase; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase; WHO=World Health Organization toxicity scale.

†In 13 patients.

‡In 12 patients.

the end of IPL. This was followed by a rhabdomyolysis requiring several fasciotomies. The systemic and hemodynamic responses to rTNF-α following IPL could therefore not be evaluated in this patient, thus leaving 18 evaluable patients.

Patterns of Shock During the Postoperative Period

During the early postoperative phase, 17 of the 18 evaluable patients (94%) presented a shock unresponsive to fluid challenge, requiring the continuous perfusion of vasopressor or vasopressor and inotropic agents, 1 to 10 h after the administration of rTNF-α through IPL. In one patient, a young athletic man, hypotension responded to a massive fluid challenge only: blood (9 U), fresh frozen plasma (3 U), hydroxyethylstarch (2,000 mL), and crystalloids (8,000 mL). Nine patients had a distributive shock, while a mixed shock was found in eight other patients. Patients with a distributive shock required noradrenaline earlier than those with a mixed shock (4 h vs 6% h after rTNF-α), but the ranges did not differ (1 to 11 h vs 2 to 10 h, respectively) (Table 2). In the patients with a mixed shock, dobutamine therapy was required after a mean delay of 9 h (range, 1 to 16 h) after rTNF-α administration. All patients recovered from their shock within 46 ± 22 h, although all had a persistent hyperdynamic state for several additional days (Fig 1).

Delivery, Uptake of Oxygen, and Pulmonary Gas Exchanges

The oxygen parameters were mainly characterized by an increase in both Do2 and Vo2. In most patients, the O2 extraction ratio was reduced during the phase of shock, and this abnormality persisted for 24 to 48 h until removal of the pulmonary artery catheter. Patients required mechanical ventilation for a mean of 3 days (range, 1 to 5 days). Transient bilateral interstitial or mixed infiltrates were documented in all patients on the chest radiographs during the first 2 days after IPL. The PaO2/FIo2 ratio was below 200 in seven patients, but none presented the full ARDS criteria.

Other Systemic and Local Effects

Temperature peaked up to 38.4°C in 12 patients (67%) without chills (Table 3). Fourteen patients (78%) had an initial transient (3 to 6 h) fall in WBC count (<4.0 giga/L), including neutropenia (neutrophils <1.0 giga/L) in 6 of them (43%). Despite severe perturbation of the parameters of coagulation, a disseminated intravascular coagulation (DIC) was documented in one patient only. These hematologic perturbations returned to normal within 72 h, with the exception of the thrombocyte counts that returned to normal after 5 to 7 days only. These alterations were not associated with clinically significant
hemorrhage; however, it must be mentioned that all these patients did receive several units of fresh frozen plasma. Nine patients (50%) had some liver toxic reactions, consisting mainly of slight cytolysis or hyperbilirubinemia (Table 3). Four patients (22%) had a fall in creatinine clearance, which was transient. Tubular necrosis related to shock did not occur. All perfused limbs presented an important localized reaction characterized by a large lymphedema, diffuse erythema, and progressive necrosis of the tumor.

Development of Infection

An infection requiring a modification of the antibiotic prophylaxis was documented in 11 patients (61%). Six patients developed microbiologically documented bronchopneumonia, characterized by purulent sputum (Gram-negative bacilli in five, Gram-positive cocci in one) and a chest radiograph with new infiltrates. In three other patients, bronchopneumonia was diagnosed on clinical grounds only. These episodes were treated with a third-generation cephalosporin or with amoxicillin/clavulanate. Two patients had a superinfection of the necrosed tumor (Pseudomonas aeruginosa in one patient and Staphylococcus aureus in the second).

Circulating TNF-α Levels

Bioactivity of TNF in the blood during the IPL and in the systemic circulation after tourniquet removal were measured in 12 patients (Table 4). The results demonstrated an early massive leakage from IPL to the systemic circulation. However, no apparent correlation was observed between TNF-α levels measured in the systemic circulation and either the type or the duration of shock. Six of 12 patients had a peak higher than 100,000 pg/mL. The characteristics of the shock in the six patients with levels >100,000 pg/mL did not differ from the characteristics of the other six patients.

Discussion

Major systemic changes were observed in all patients receiving a combination of rTNF-α, rIFN-γ, and melphalan in hyperthermic IPL for in transit metastasis of melanoma or sarcoma. These were mainly characterized by acute circulatory failure mimicking septic shock associated with disturbances of gas exchanges, a drop of blood cell counts, and abnormal results liver function tests. Two main mechanisms must be considered to explain these findings: first, the effect of TNF-α, IFN-γ, or melphalan during and following IPL, and second the effect of the hyperthermic IPL per se.

Hemodynamic Response

In the present study, all patients had a shock starting soon following cytokine administration. This required immediate and important fluid resuscitation and vasopressor administration. Early circulatory failure during such procedure can be attributed to systemic leakage of rTNF-α. Indeed, very high systemic rTNF-α levels were found in 12 patients, indicating early and important rTNF-α leakage throughout IPL. In previous study, significant although variable TNF leakage during IPL was shown. Surprisingly, major systemic side effects were uncommon, but there was a correlation between the magnitude of leakage and the systemic toxic reactions. Hypotension occurred in 13% of patients, but quickly recovered under low dopamine and fluid support, without reaching the usual shock criteria. In a recent review on clinical trials using IPL with TNF-α, Fraker and Alexander mentioned that among patients treated at the National Cancer Institute, approximately one third required postoperative vasopressor support. However, no detailed data on the population and on the systemic response are yet published. There are two possible explanations for this discrepancy. First, in our study, we used a higher limb perfusate flow that was probably responsible for higher limb venous pressure, thus favoring rTNF-α leakage in systemic circulation during IPL. Second, the washout performed at the end of IPL may have been insufficient to eliminate the added drugs. We recently performed IPL using perfusate flow reduced to 45 mL/L of perfused limb and increased washout volume to 6 to 10 L; these changes resulted in milder hemodynamic and systemic side effects in the first patients.

Overall, all patients but one had circulatory failure requiring aggressive management. Analysis of hemodynamic data showed two distinctive patterns: a pure distributive shock, requiring fluid replacement and norepinephrine support, or a mixed distributive and cardiogenic shock, requiring fluid, vasopressor, and inotropic agents. Interestingly, a history of cardiac disease was more common in the second group of patients. The hemodynamic pattern found in our patients was very similar to that observed during septic shock. Indeed, typically a hyperdynamic, distributive cardiovascular state with low systemic vascular resistances, normal or increased CO, tachycardia, and elevated pulmonary O₂ saturation is found in more than 90% of patients with established septic shock. Moreover, both experimental and clinical studies have shown that myocardial function is rapidly altered in the course of septic shock. This can be observed in a patient with low, normal, or high cardiac output. This was also the case in our patients, 47% of them requiring dobutamine to improve the cardiac function.

In the present study, systemic O₂ utilization was
affected by the IPL. The perturbation was characterized by high DO2 and VO2, associated with low O2 extraction ratio. As for hemodynamics, similar findings are observed during sepsis syndrome and septic shock. Interestingly, in our patients, this change in body O2 utilization was more prolonged than the shock period. Since this low O2 extraction ratio was not associated with significant lactic acidosis, it suggests that systemic O2 debt was not prominent.

**Systemic Effects of IPL**

Hyperthermic IPL has become the established mode of therapy for regionally advanced melanoma and sarcoma. It allows the administration of high doses of drugs in a closed system with acceptable local toxic reactions. From their cumulative experience on 1,509 courses of chemotherapy through IPL, the group who described the method more than 30 years ago reported some local side effects but very limited systemic effects attributable to this technique. Thus, it is likely that the systemic effects that were observed in the present study could not be attributed either to the hyperthermic IPL or to the melphalan.

**Systemic Effects of INF-γ**

Interferon gamma has direct antiproliferative activity against some human tumor cells and was added for its potential synergy with TNF-α. In the present study, the main purpose of its administration was to raise the number of TNF receptors on tumor cells. Compared with the systemic effects of rTNF-α, administration of rIFN-γ is associated with less severe toxic reactions. Fever and moderate cardiovascular manifestations commonly occur in patients receiving this agent. Although concomitant administration of rIFN-γ and TNF-α has been shown to increase the side effects, the latter were mainly attributed to rTNF-α in a preliminary analysis of a phase 2 study. The design of this study makes it difficult to determine the relative importance of TNF-α and IFN-γ in the systemic effects we observed.

**Systemic Effects of TNF-α**

The systemic effects of TNF administration have been well described. In patients with cancer severe systemic effects occurred after the administration of 200 to 300 μg/m² rTNF-α, and consisted of fever (41°C), hypotension, dyspnea, abnormalities of the liver function test results, thrombocytopenia, and leukopenia. Many of the systemic manifestations observed in our patients after high-dose rTNF-α administration through IPL are consistent with these previous observations. The severe distributive shocks observed, requiring aggressive supportive therapy, including very high amounts of fluids and vasopressor, were not unexpected with large TNF leakage. To our knowledge, they have not been reported previously in other published series.

It is well established that among cytokines, TNF-α is one of the major mediators of the cascade of events leading to the multiple dysfunctions related to septic shock. Pretreatment with antibodies against TNF-α has been shown to prevent death in mice and in primates challenged with endotoxin or with live microorganisms. In human volunteers challenged with small doses of endotoxin (4 ng/kg), serum TNF levels reached 100 pg/mL. In patients with documented septic shock, persistent TNF-α levels of up to 200 to 300 pg/mL correlated with fatal outcome. Recent high levels of TNF-α have been reported among patients with fatal meningococcemia (500 to 3,500 pg/mL). A recent article reported extremely high levels of TNF-α (9,157 pg/mL) in a man who survived to severe shock with mild organ dysfunctions after self administration of 15,000 ng/kg of purified endotoxin. The serum levels of TNF-α (1,760 to 365,440 pg/mL) found in our patients at the end of IPL in the systemic circulation are among the highest reported in the literature and were probably related to rTNF-α release from the limb tissues after the end of IPL. All but one patient developed a septic-like shock, but the absence of correlation between the levels of TNF-α and the systemic effects may indicate that the systemic response to TNF-α could depend on other factors, such as the presence of endotoxin or of other circulating cytokines.

None of our patients died. This strongly contrasts with the 50% mortality rate repeatedly reported in patients with detectable levels of circulating TNF-α in septic shock of various causes. These data suggest that factors other than TNF-α may be responsible for the fatal outcome observed in septic shock.

**Conclusion**

Major systemic effects, consisting mainly of cardiovascular, respiratory, and hematologic disturbances resulted from TNF-α leakage in patients after IPL with high-dose of recombinant TNF-α. Although not correlated with the levels of TNF-α found in the systemic circulation, the most striking side effect consisted of a prolonged septic shock-like syndrome requiring aggressive management. All organ failures resolved within 2 to 5 days and all patients survived without sequelae.
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