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Anesthesiologists' Management of Isolated Limb Perfusion with "High-dose" Tumor Necrosis Factor α

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TUMOR necrosis factor α (TNF_α) is a polypeptide cytokine produced mainly by activated monocytes. It possesses a broad spectrum of biologic properties, and is one of the most important mediators of multiple-organ system response in endotoxic and septic shock.[1] Human recombinant TNF_α has been shown to have antitumor activity against advanced malignant tumors in humans.[2] However, because of severe systemic side effects of clinically effective doses in patients with cancer, the results of phase I clinical trials have been disappointing. The maximum tolerated single dose in humans, administered systemically, is only 250–350 $\mu g/m^2$, which is less than that needed to reach a significant antitumor effect.[2] Side effects of recombinant TNF_α described during systemic treatment of cancer in humans include: fever up to 41° C (63% of cases), hypotension (48%), dyspnea (23%), chest tightness (10%), and peripheral cyanosis (40%).[3] In addition, abnormalities of liver function, thrombocytopenia, malignant hyperthermia, cardiovascular collapse with unrecordable blood pressure, peripheral capillary leak syndrome, acute renal failure, and bleeding into a brain metastasis with fatal outcome have also been reported as side effects of recombinant TNF_α treatment in humans.[2–6]

Isolated perfusion of limbs with high doses of cytotoxic drugs is an established treatment modality in severe forms of melanoma and sarcoma. It allows the use of 10 to 20 times higher doses of antitumor drugs than would be tolerated systemically. This method was used by Lienard *et al.* to administer high-dose recombinant TNF_α together with interferon τ (IFN_τ) and the alkylating agent, melphalan, both of which have been shown to increase the antitumor activity of TNF_α.[2,7] The clinical results of this study and other phase II clinical trials are quite promising for patients with advanced malignant melanoma or sarcoma on the extremities.[7] Approximately 85% complete remission and 15% partial recurrence have been reported in patients with metastatic melanoma, and the rate of limb sparing has been as high as 92%.[7] Thus, it is more than likely that anesthesiologists will be increasingly involved in this kind of therapy, as well as dealing with the severe side effects of this treatment. We discuss below the anesthetic management of this procedure, together with a case of a severe "septic-shock-like" reaction causing multiple-organ system dysfunction in a patient treated

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with this triple-drug regime (TNF_α–IFN_τ–melphalan) for a sarcoma.

Case Report

A 62-yr-old man (body weight 75 kg) with a history of hypertension was admitted for cytotoxic perfusion with high-dose recombinant TNF_α (combined with IFN_τ and melphalan) of a rhabdomyosarcoma on his left leg. Preoperative clinical and laboratory evaluation revealed no significant abnormalities. Anesthesia consisted of etomidate, fentanyl, pancuronium, and isoflurane in N_2O/O_2: 2/1. The left radial artery was cannulated for monitoring of blood pressure (mean arterial pressure (MAP); mmHg) and a balloon-tipped pulmonary artery catheter with a thermistor was introduced for monitoring of central venous pressure (CVP; mmHg), pulmonary artery pressure (PAP; mmHg), cardiac index (CI; $l \cdot min^{-1} \cdot m^{-2}$) and pulmonary capillary wedge pressure (PCWP; mmHg). Other monitoring included continuous ECG; pulse oximetry (SpO_2; %); continuous inspired and expired concentrations of CO_2, O_2, N_2O, and isoflurane (%); peak inspiratory and end-inspiratory airway pressures (cm H_2O); intermittent calculations of the total compliance (chest wall and lung, C_T; ml/cm H_2O, *i.e.*, tidal volume divided by the end-inspiratory pressure minus PEEP); and hourly urine output.

Shortly after induction of anesthesia, an intravenous infusion of 50 mg indomethacin was administered over 3 h, followed by 200 mg over 21 h. Before cannulation (silicon tubing) of the femoral vessels, 15,000 IU heparin was given intravenously, and a continuous infusion of dopamine (3.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was started. A bubble oxygenator was used, and the priming consisted of 25 ml sodium bicarbonate 8.5%, 2,500 IU heparin, 1,000 ml gelatin (a synthetic colloid, Haemacel; Behringwerke, Marburg, Germany), and one unit of packed red blood cells (RBCs). During the perfusion, 4.0 mg of recombinant TNF_α, 0.2 mg recombinant interferon τ (both provided by Boehringer-Ingelheim, Ingelheim am Rhein, Germany), and 85 mg melphalan (Alkeran, Burroughs Wellcome, London, UK) were added into the perfusate. Estimation of the degree of leakage of cytotoxic drugs into the systemic circulation was made with 99m Technetium-labeled human albumin. It was injected into the extracorporeal circuit, and radioactivity was measured in samples taken from the radial artery cannula every 5 min during the 90-min procedure. At the end of the perfusion, the leg was perfused with 1,000 ml dextran 40 (Rheomacrodex; Pharmacia, Uppsala, Sweden) and 1,000 ml of Ringer's lactate (RL) through the extracorporeal pump. At the same time, 500 ml of RL and 500 ml of 5% human albumin (Albumin 5%; Central-laboratories, Bern, Switzerland) were slowly given intravenously to raise the PCWP from 9 to 12 mmHg before releasing the tourniquet.

The patient's condition remained stable throughout the perfusion, except for systemic blood temperature that increased from 37.1 to 37.6° C. Leakage of perfusate into the systemic circulation, as measured by radiolabeled albumin, was highest after 60 min (3.0%). Approximately 5 min after releasing the tourniquet, the SpO_2 decreased to 85%, and the systemic blood pressure decreased to less than 100 mmHg (fig. 1). Isoflurane was discontinued, 100% oxygen was administered, PEEP increased from 2 to 5 cm H_2O, 500 ml gelatin was rapidly given intravenously, and dopamine infusion increased to 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$. However, during the next 15–20 min, there was a continuous decrease in SpO_2 (from 85 to 65%), MAP (from 70 to 45 mmHg), and PCWP (from 12 to 7 mmHg). There was also a continuous increase in mean PAP (from 20 to 33 mmHg), CI (from 2.9 to 6.1 $L \cdot min^{-1} \cdot m^{-2}$), and HR (from 63 to 110 beats/min) (fig 1). During this time, one unit of packed RBCs and more intravenous fluids were administered (1,000 ml RL, 500 ml albumin 5%, and 1,000 ml gelatin). PEEP was increased to 10 cm H_2O, and the dopamine infusion increased to 20, 30, and 50 $\mu g \cdot kg^{-1} \cdot min^{-1}$ without apparent effects. Repeated intermittent intravenous bolus injections of 100–200 μg phenylephrine increased the MAP by 5–10 mmHg for a few minutes each time, but the SpO_2 remained low (65%–70%). By this time, the total compliance had decreased (from 55 to 35 ml/cm H_2O), the temperature had increased to 38.3° C, and the PCWP had increased from 7 to 18 mmHg. Clinically severe septic shock was suspected. The patient was febrile, the skin was warm, and the patient had a hyperdynamic circulation with severe hypotension and tachycardia, but no obvious cyanosis. During the next 30 min, pentoxifylline (Trental; Hoechst, Frankfurt, Germany) 1.5 mg/kg was given by intravenous infusion. By the end of the infusion, MAP, PAP, PCWP, and SpO_2 had all improved markedly (fig. 1) and 30 min later MAP was 65 mmHg, PAP was 23 mmHg, PCWP was 12 mmHg, and SpO_2 was 88%, while the body temperature and cardiac index remained elevated.

After arrival at the ICU, mechanical ventilation was continued, and 50% inspired oxygen and 7.5 cm H_2O PEEP were required to keep $SpO_2 \geq 93\%$. Arterial blood gases were normal, except for slight metabolic acidosis. MAP was 75 mmHg, with 5–7.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dopamine and 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ pentoxifylline. Hemoglobin had decreased from a preoperative value of 15.7 to 6.4 g/dl, despite an estimated intraoperative blood loss of only 1,000 ml (replaced with one unit of RBCs); leukocyte counts had decreased from 5.2 to 0.8 $\times 10^{12}$/l; platelet counts had decreased from 328 to 64 $\times 10^{12}$/l; bilirubin had increased from 9 to 49 μg/l; liver transaminases and alkaline phosphatase had increased three to five times; and coagulation tests were severely abnormal (table 1). The patient had oliguria only for a few hours, and urea was only slightly elevated.

Twenty hours after admission to the ICU, mechanical ventilation was discontinued and, after tracheal extubation, the patient had normal blood gases while receiving oxygen 3–4 l/min through a nasal catheter. The body temperature was 36.9° C, urine output was more than 100 ml/h, and the circulation was stable even after discontinuing dopamine and pentoxifylline infusions. Liver transaminases were still elevated, bilirubin had increased further to 130 μg/l, and platelet counts remained low. The patient was then transferred to an intermediate care unit before going to the floor on the second postoperative day. When the patient went home on the eighth postoperative day, the liver function tests, platelet counts, and coagulation tests were still abnormal, but considerably improved. Seven weeks later, when the patient returned to have the necrotic tumor surgically removed, he was in good general health and all routine tests were normal. The tumor that was removed was 90% necrotic according to the histopathologic report.

Discussion

Most of the information on the effects of high-dose TNF_α has been obtained from experimental studies. Fever, pulmonary dysfunction (hypoxemia, decreased lung compliance, and pulmonary hypertension), and hyperdynamic circulatory shock (low systemic vascular

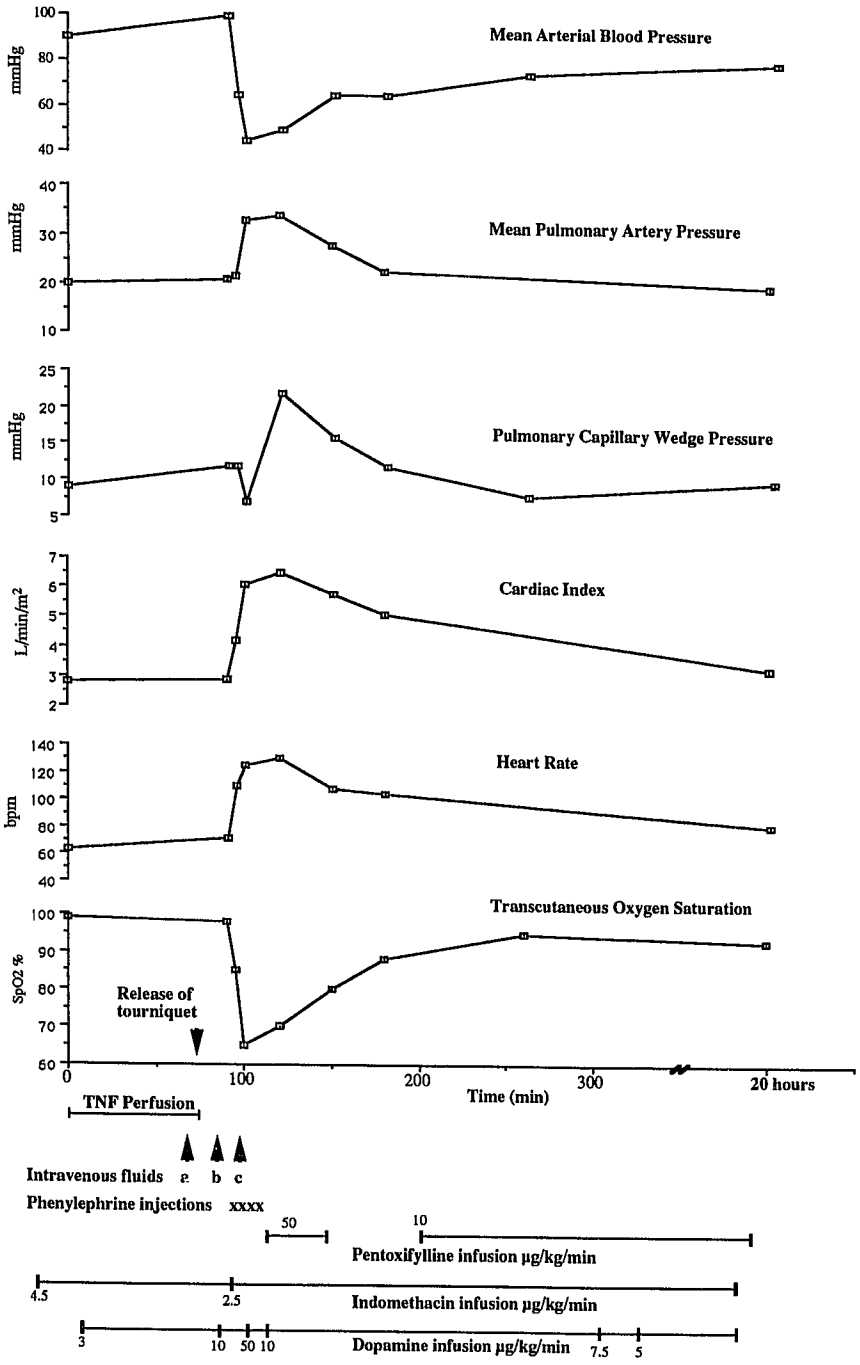

Fig. 1. Changes in hemodynamics and SpO_2 during and after isolated limb perfusion with high-dose TNF_α. Note the abrupt changes occurring after release of the tourniquet and the lack of response to large amounts of intravenous fluids and pressure drugs. But, after intravenous infusion of pentoxifylline hemodynamic and respiratory variables improved markedly. (*a*) Intravenous infusion of 500 ml of 5% albumin and 500 ml of Ringer's lactate. (*b*) One unit of RBCs, 500 ml of gelatin, and 1000 ml of Ringer's lactate. (*c*) Five hundred milliliters of 5% albumin and 1000 ml of gelatin. (*x*) Repeated intermittent intravenous bolus injections of 100–200 µg phenylephrine.

resistance and high cardiac output) are the most obvious early effects of high-dose TNF_α in animals,[2,8–10] as well as in endotoxemia and early septic shock.[11–12] Other organ systems, such as the kidneys, liver, intestine, and coagulation system, are affected, as well, but clinical signs and symptoms frequently appear later.[7,12] The patient described above developed most of these symptoms and signs. He had a severe decrease in SpO_2 and arterial blood pressure, while CI and PAP were high. Later, abnormal liver and coagulation tests, as

Table 1. Laboratory Data

	Hemoglobin ($g \cdot dl^{-1}$)	Platelet Count ($10^{12} \cdot l^{-1}$)	WBC ($10^{12} \cdot l^{-1}$)	Total Bilirubin (μM)	GOT–AST ($U \cdot l^{-1}$)	GPT–ALT ($U \cdot l^{-1}$)	PTT (s)	PT (%)	Creatinine (μM)
Preoperative	15.7	328	5.2	9	15	12	26	98	109
1 h after surgery	6.4	64	0.8	49	45	50	55	35	104
1 day after surgery	9.9	71	9.1	130	65	45	45	51	91

WBC = white blood cell (leukocyte) count; PTT = partial thromboplastin time; PT = prothrombin time.

well as a severe decrease in leukocyte and platelet counts, indicated multisystem injury.

According to the available literature, severe toxicity associated with the triple-drug regime (TNF_α–IFN_γ–melphalan) is primarily caused by TNF_α, and not by IFN_γ or melphalan.[2,7] To reduce the occurrence of severe toxic reactions during TNF_α treatment, every precaution has to be made to keep circulation of the limb isolated during the perfusion by using a high-pressure tourniquet and frequently monitoring the amount of spillover, *e.g.*, by radiolabeled albumin. Still, there is always some leakage to the systemic circulation, and in our patient it was 3%, which is, in fact, rather low.[7] In addition, despite a thorough washout of the circulation in the perfused extremity at the end of the procedure, there is still a risk of severe systemic reaction from TNF_α, as was the case in our patient, who did not show much systemic effect until a few minutes after release of the tourniquet. In fact, it has recently been shown that, because of TNF_α-induced capillary injury in the perfused leg, about 50% of radiolabeled albumin remains in the leg after a thorough washout of the circulation.[7,13] This indicates that TNF_α also leaks through the injured endothelium and may, therefore, reenter the systemic circulation at a later stage through the lymphatics and cause systemic effects. It is also known that TNF_α is not metabolized in peripheral tissues, but neutralized by naturally occurring soluble TNF_α receptors that reach a peak concentration in the blood about 2 h after exposure to TNF_α. This is followed by conjugation in the liver, and the final excretion of metabolites goes through the kidneys.[7,13]

Pharmacologic agents that may ameliorate the side effects of TNF_α, such as inhibitors of arachidonic acid metabolism, have been used for TNF_α prophylaxis. Indomethacin, an inhibitor of the cyclooxygenase pathway, has been shown to block toxic effects of high-dose TNF_α in pigs. In addition, ketoprofen, which is a dual inhibitor of cyclooxygenase and lipoxygenase, has been reported to ameliorate cardiovascular and respiratory effects of endotoxin in animals and prevent TNF_α induced hypotension in humans.[3,14–16] Although indomethacin did not have obvious effects in our patient, this does not mean that inhibitors of arachidonic acid metabolism should be regarded as useless under these circumstances. The doses we used may have been too low, or the treatment started too late, to have the anticipated effects. Perhaps a dual inhibitor like ketoprofen, given several hours before surgery, may turn out to be more effective. Furthermore, Lejeune *et al.* recommended the use of low-dose dopamine during and after TNF_α perfusion to decrease the risk of cardiovascular side effects.[7]

Pentoxifylline, which is a methylxanthine derivative and inhibitor of phosphodiesterase, was introduced more than a decade ago for its effects on blood rheology and microvascular blood flow in patients with occlusive arterial disease. It has also been shown that pentoxifylline has effects on many cellular systems, which are believed to play a role in the pathophysiologic events occurring during thrombosis, ischemia, acute inflammation, and sepsis, such as monocytes, neutrophils, platelets, and endothelial cells.[17–21] Experimental studies have demonstrated beneficial effects of pentoxifylline in hemorrhagic shock, bacterial peritonitis, and tumor necrosis factor-induced lung injury.[18–20] In a new study, pentoxifylline markedly decreased both lung and liver platelet sequestration, and improved gas exchange during endotoxemia.[17] In addition, Zabel *et al.* showed that pentoxifylline lowers plasma concentrations of TNF in human volunteers exposed to endotoxin.[21] However, because of the potential risk of diminishing the antitumor effects of TNF_α, pentoxifylline has, to our knowledge, not been used before in patients undergoing TNF_α treatment for cancer.

Considering the time relationship between the administration of pentoxifylline and improved clinical condition of our patient, the wide variety of cellular effects of pentoxifylline, and its documented effects on TNF_α toxicity in animals and humans, it appears likely

that our patient benefited from pentoxifylline therapy. However, it does not appear that the pentoxifylline treatment interfered significantly with the antitumor therapy, because 90% of the tumor was necrotic (which is quite high for sarcomas) when it was surgically removed 7 weeks after the perfusion therapy. In the future, soluble TNF_α receptors or TNF_α antibodies may become the treatment of choice for the most severe life-threatening side effects of TNF_α, but this treatment may decrease the efficiency of the antitumor treatment.

Because the treatment of malignant tumors with TNF_α–IFN_γ–melphalan appears to be quite effective in clinical settings, it is likely to be continued in some form, despite the frequent occurrence of side effects. Thus, it is probable that an increasing number of anesthesiologists will be dealing with these problems in the future, and must, consequently, be acquainted with all possible toxic effects of the treatment. Currently, there are no pharmacologic agents available that completely prevent systemic toxic effects of TNF_α without interfering with the cancer treatment. However, pretreatment with cyclooxygenase inhibitors or dual inhibitors of cyclooxygenase and lipoxygenase may attenuate some severe reactions to TNF_α. In addition, pentoxifylline has documented anti-TNF_α effects, and may, therefore, also be useful as prophylaxis or for treatment of severe systemic effects of TNF_α. It is evident that, because of the severity of the side effects, the patients should be carefully selected in regard to general health before being accepted for TNF_α treatment, and invasive monitoring during surgery is required. Because serious systemic side effects can also be expected postoperatively, close observation and hemodynamic monitoring should be maintained into the postoperative period.

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