Systemic side effects of isolated limb perfusion with tumor necrosis factor alpha
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High plasma levels of tumor necrosis factor alpha and shortlived sepsis syndrome in patients undergoing hyperthermic isolated limb perfusion with recombinant tumor necrosis factor alpha, interferon gamma and melphalan

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High plasma tumor necrosis factor (TNF)-α concentrations and a sepsis-like syndrome in patients undergoing hyperthermic isolated limb perfusion with recombinant TNF-α, interferon-γ and melphalan

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Summary

This chapter describes the post-operative course of 25 consecutive patients, who underwent hyperthermic isolated limb perfusion with recombinant tumor necrosis factor α (r-TNF-α) and melphalan, following pretreatment with recombinant interferon gamma (r-IFN-γ), as treatment for recurrent melanoma, primary nonresectable soft tissue tumors, planocellular carcinoma or metastatic carcinoma. It is a retrospective, descriptive study, relating systemic TNF-α levels with indices of disease severity.

All patients developed features of sepsis syndrome and required intensive care treatment. Most patients recovered quickly with a median ICU stay of 2 days (range 1-25). Maximum systemic TNF-α levels ranged from 2284 to 83000 ng/L (median 25409 ng/L) and returned to baseline values within 8 hours. Despite these high levels of TNF-α no patient died in the ICU, although the patient with the highest TNF-α level developed multiple organ failure and required continuous venovenous hemofiltration for 16 days.

Linear regression analysis showed a positive correlation between maximum TNF-α levels and systemic vascular resistance (p<0.01), cardiac index (p<0.02), lung injury score (p<0.02), prothrombin time (p<0.02) and activated partial thromboplastin time (p<0.05). It is concluded that hyperthermic isolated limb perfusion with r-TNF-α leads to high systemic levels of TNF-α, probably due to leakage of r-TNF-α from the perfusion circuit, mainly through collateral bloodflow. A sepsis like syndrome is seen in all patients. Despite high levels of systemic TNF-α, this sepsis syndrome is short-lived and recovery is rapid and complete in most patients.
Sepsis syndrome in isolated limb perfusion with TNF-α

Introduction

The cytokine TNF-α, originally defined by its antitumor activity in vivo, is now recognized to play a key role as a polypeptide mediator in the pathogenesis of septic shock [1-7]. TNF-α has been shown to cause myocardial depression, vasodilation, and diffuse lung injury in animal studies [8-10]. Levels of TNF-α in the serum of septic patients show a positive correlation with the severity of illness and mortality [11-14]. Cardiovascular, and fibrinolytic responses to the administration of endotoxin and TNF-α have also been described in volunteer studies, although the severity of symptoms has limited the dose used [15-18].

With hyperthermic isolated limb perfusion a very high dose of a cytostatic agent can be administered locally in a limb while minimizing systemic toxicity. A combination of r-TNF-α, r-IFN-γ and melphalan was used in 25 patients with, mostly, primary nonresectable soft tissue tumors and melanomas stage III A/AB of the limb, as an alternative to amputation. This triple combination with hyperthermia was chosen because of the reported synergistic antitumor effect of r-TNF-α with r-IFN-γ, hyperthermia, and alkylating agents [19]. We have studied the clinical course of these patients and its relationship to leakage of r-TNF-α to the systemic circulation during perfusion.

Subjects and methods

Subjects

Between January 1991 and June 1993, 25 patients received hyperthermic isolated limb perfusion at the Division of Surgical Oncology of the Groningen University Hospital, after approval of the Medical Ethics Committee and informed written consent had been obtained. Tumor histology is summarized in Table 1.

<table>
<thead>
<tr>
<th>TUMOR HISTOLOGY</th>
<th>NUMBER OF PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant Melanoma</td>
<td>7</td>
</tr>
<tr>
<td>Liposarcoma</td>
<td>4</td>
</tr>
<tr>
<td>Malignant Fibrous Histiocytoma</td>
<td>3</td>
</tr>
<tr>
<td>Epithelioid Sarcoma</td>
<td>3</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>2</td>
</tr>
<tr>
<td>Myxoid Chondrosarcoma</td>
<td>1</td>
</tr>
<tr>
<td>Malignant Schwannoma</td>
<td>1</td>
</tr>
<tr>
<td>Neurofibrosarcoma</td>
<td>1</td>
</tr>
<tr>
<td>Embryonal Rhabdomyosarcoma</td>
<td>1</td>
</tr>
<tr>
<td>Planocellular Carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Metastatic Renal Cell Carcinoma</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 1 Tumor histology.
Four additional patients underwent hyperthermic isolated limb perfusion without pretreatment with r-IFN-γ and without the addition of r-TNF-α to the perfusate.

Anesthesia and intensive care
Anesthesia was induced with thiopental, after which the patients were paralyzed with vecuronium and the trachea intubated. Anesthesia was maintained with midazolam, sufentanyl, nitrous oxide and isoflurane. After induction arterial and pulmonary artery catheters were inserted. Blood pressure, ECG, urine output, venous and pulmonary pressures, as well as pulmonary wedge pressures and blood gas values were checked at standard intervals. All patients were admitted to the intensive care unit following surgery. Patients received mechanical ventilation until hemodynamically stable. Fluid resuscitation with crystalloid and colloid solutions was given to maintain pulmonary wedge pressures above 11 mmHg and a dopamine infusion was added if systolic arterial blood pressure fell to 90 mmHg or decreased by > 30 mmHg from preoperative values despite adequate fluid replacement.

Isolated Limb Perfusion
For two days prior to the perfusion patients received 0.2 mg r-IFN-γ subcutaneously. The perfusion technique employed at the Groningen University Hospital is based on the technique developed by Creech and Krementz [20]. Briefly, after ligation of all collateral vessels and heparinization of the patient with 3.3 mg heparin/kg bodyweight (Thromboliquine, Organon BV, Oss, The Netherlands) the axillary, iliac, femoral or popliteal vessels were dissected, cannulated and connected to the extracorporeal circuit. The perfused limb was wrapped in a thermal blanket to reduce heat loss and four thermistor probes were inserted subcutaneously and intramuscularly for continuous monitoring of the temperature during perfusion. A tourniquet was applied to the proximal limb in an attempt to minimize leakage of the perfusate into the systemic circulation through skin collaterals. Perfusion was performed during 90 minutes under mild hyperthermic conditions (39-40°C). The perfusate consisted of 350 ml 5% dextran 40 in glucose 5% (Isodex, Pharmacia AB, Uppsala, Sweden), 500 ml blood (250 ml red blood cells, 250 ml plasma), 30 ml 8.4% NaHCO₃ and 0.5 ml 5000 IU/ml heparin (Thromboliquine). The perfusate was oxygenated with a bubble oxygenator and driven by a roller pump. At the start of perfusion r-TNF-α (Boehringer, Ingelheim, Germany, 4 mg for leg perfusions, and 3 mg for arm perfusions) and 0.2 mg r-IFN-γ (Boehringer, Ingelheim, Germany) were injected as a bolus into the arterial line of the perfusion circuit. Melphalan (Burroughs Wellcome, London, England, 10 mg/L volume of an affected leg and 13 mg/L volume of an affected arm) was administered 30 minutes later. During perfusion potential leakage to the systemic circulation was monitored with I¹³¹ labeled albumin [23]. After 90 minutes of perfusion, the limb was flushed with 2 L dextran 40 in glucose 5% (Isodex) and 500 ml blood (250 ml red blood cells, 250 ml plasma), catheters were removed, the circulation restored and the heparin antagonized with protamine chloride. A lateral fasciotomy of the anterior compartment of the lower leg was performed in leg perfusions or a fasciotomy of the forearm in arm perfusions to prevent a compartment syndrome.

Four additional patients underwent hyperthermic isolated limb perfusion with melphalan in exactly the same way but without the addition of r-TNF-α to the perfusate and without pretreatment with r-IFN-γ.
**Hemodynamic measurements**

Hemodynamic variables were measured immediately after the patient had arrived in the intensive care unit and then at hourly intervals. Measured variables included the heart rate, mean arterial pressure, central venous pressure, mean pulmonary artery pressure, pulmonary capillary wedge pressure. Cardiac output, cardiac index, systemic vascular resistance and pulmonary vascular resistance were determined at two hourly intervals. Pressure transducers were set to zero at the level of the midaxillary line. Cardiac output was measured in triplicate by the thermodilution method, with the use of a cardiac output computer and cold saline.

Oxygen consumption, oxygen delivery, oxygen extraction ratio and alveolar arterial oxygen difference were calculated according to standard formulas. Lung Injury Score as a measure of Adult Respiratory Distress Syndrome was calculated from the chest roentgenogram, hypoxemia and positive end-expiratory pressure scores as described by Murray et al [21]. The APACHE II score was calculated for each patient on the basis of the worst results in the first 24 hours after admission to the intensive care unit. The Simplified Sepsis Score for each patient was calculated as described by Baumgartner et al [22].

**Assay for tumor necrosis factor**

TNF-α levels were determined by specific immunoradiometric assay (Medgenix Diagnostics, Soesterberg, the Netherlands). Samples were processed according to the guidelines of the manufacturer. Blood samples (3 ml) from a indwelling radial artery cannula were collected in EDTA vacutainer tubes, and kept on melting ice during transport to a centrifuge. Samples were centrifuged for 10 min at 3000 rpm at 0°C and the separated plasma kept at -20°C until analysis. A baseline sample was taken for TNF-α assay after the insertion of the arterial line, then at 5, 30, 60, and 89 minutes after the start of the perfusion. Samples from the extracorporeal circuit were also taken at the same sampling times. After restoration of circulation to the perfused limb, systemic samples were taken at 1, 5, 10, 30 and 60 minutes after removal of arterial clamps, hourly thereafter for at least eight hours and finally the next morning.

**Statistical analysis**

Data were analyzed using SPSS for MS WINDOWS (release 5.0). Results are tabulated to show preoperative values, mean values, standard error of the mean, and range. Correlations were sought between variables and maximum TNF-α levels. A p-value < 0.05 was considered significant.

**Results**

**Demographic Data**
Eleven male and fourteen female patients were studied (mean age 49.2 years, range 18-74 yrs). Twenty three perfusions of the lower limb were performed (iliac vessels cannulated in 15 patients, femoral or popliteal vessels cannulated in 8 patients). Two perfusions of the upper limb were performed. Histology of the tumors is summarized in Table 1. All perfusions were performed without technical complications. Leakage from the perfused limb circuit ranged from 0 to 8% (median 2%).
Clinical Course

All patients developed clinical sepsis syndrome with fever, rise in cardiac output, fall in systemic vascular resistance and the need for fluid resuscitation and inotropes. Maximum temperature, APACHE II scores, Simplified Sepsis Scores, Lung Injury scores, fluid balance, maximum dopamine requirements in the first 24 hrs of Intensive Care Unit (ICU) stay, and length of ICU stay are summarized in Table 2 and 3. One patient developed multiple organ failure and required continuous venovenous hemofiltration for 16 days.

All 4 patients who received hyperthermic isolated limb perfusion with melphalan only (i.e. without r-TNF-α) did well without invasive hemodynamic monitoring. They did not need large infusions of fluid or continued treatment with dopamine and were not admitted to the ICU.

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>MEAN</th>
<th>SEM</th>
<th>RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay (days)</td>
<td>3*</td>
<td></td>
<td>1-25</td>
</tr>
<tr>
<td>Maximum temperature (°C)</td>
<td>40.0</td>
<td>0.12</td>
<td>39.0-41.8</td>
</tr>
<tr>
<td>APACHE II Score</td>
<td>15.6</td>
<td>0.66</td>
<td>11-22</td>
</tr>
<tr>
<td>Simplified Sepsis Score</td>
<td>4.9</td>
<td>0.4</td>
<td>1-9</td>
</tr>
<tr>
<td>Fluid Balance 1ST 24HRS (L)</td>
<td>+10.15</td>
<td>0.87</td>
<td>+2.43 - +18.93</td>
</tr>
<tr>
<td>Time to Extubation (days)</td>
<td>2*</td>
<td></td>
<td>0-21</td>
</tr>
</tbody>
</table>

SEM, standard error of the mean.

*nonparametric distributed variable, therefore mean value should be read as median and no standard error of the mean is given.

Table 2 Clinical course data.

TNF-α levels

Systemic TNF-α levels were measured in 13 patients. Maximum TNF-α levels ranged from 2284 to 83000 ng/L (median 25409 ng/L). TNF-α levels peaked towards the end of the isolated limb perfusion and immediately after reperfusion of the limb. Levels then rapidly declined over the next hours of measurement (Figure 1).

TNF-α was detected in plasma up to 8 days after perfusion, but at very low levels. In the 4 patients who were treated with hyperthermic isolated limb perfusion without pretreatment with r-IFN-γ and without the addition of r-TNF-α to the perfusate, maximum postperfusion TNF-α levels ranged form 1-53 ng/L (mean 42 ng/L, standard deviation 22 ng/L, standard error of the mean 11 ng/L).
Sepsis syndrome in isolated limb perfusion with TNF-α

Fig. 1 Median systemic TNF-α levels (straight line and black squares) with SEM and median TNF-α levels and SEM in the perfusion circuit (dotted line and open circles).

**Hemodynamic Variables**

A full set of values for cardiac output, cardiac index, systemic vascular resistance and pulmonary vascular resistance was available for 22 patients. Cardiovascular variables on admission to the ICU are summarized in Table 3.

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>BEFORE</th>
<th>MAXIMUM</th>
<th>SEM</th>
<th>RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Index (L.min/m²)</td>
<td>3.06</td>
<td>6.3</td>
<td>0.4</td>
<td>3.6-9.9</td>
</tr>
<tr>
<td>SVR dyn/sec/cm</td>
<td>1055</td>
<td>537</td>
<td>27</td>
<td>317-757</td>
</tr>
<tr>
<td>PVR dyn/sec/cm</td>
<td>n.a.</td>
<td>79</td>
<td>6</td>
<td>21-133</td>
</tr>
<tr>
<td>DO₂ (ml/min)</td>
<td>n.a.</td>
<td>759</td>
<td>49</td>
<td>420-1341</td>
</tr>
<tr>
<td>VO₂ (ml/min)</td>
<td>n.a.</td>
<td>183</td>
<td>25</td>
<td>73-401</td>
</tr>
<tr>
<td>Extraction ratio</td>
<td>n.a.</td>
<td>0.21</td>
<td>0.03</td>
<td>0.1-0.4</td>
</tr>
<tr>
<td>Max. Dopamine conc. (mg/kg/min)</td>
<td>0</td>
<td>5.1</td>
<td>0.6</td>
<td>0-10.2</td>
</tr>
<tr>
<td>AaGradient</td>
<td>n.a.</td>
<td>20.6</td>
<td>2.0</td>
<td>10-59.3</td>
</tr>
<tr>
<td>Lung Injury Score</td>
<td>0</td>
<td>0.88</td>
<td>0.2</td>
<td>0-3</td>
</tr>
<tr>
<td>Thrombocytes (x10⁹/L)(normal 150-400)</td>
<td>286</td>
<td>168</td>
<td>11</td>
<td>22-228</td>
</tr>
<tr>
<td>Fibrinogen (g/L)(normal 1.7-3.5)</td>
<td>4.3</td>
<td>2.2</td>
<td>0.3</td>
<td>0.9-5.2</td>
</tr>
<tr>
<td>PT (sec)(normal 11-16)</td>
<td>13.7</td>
<td>22.7</td>
<td>1.4</td>
<td>14.9-34.5</td>
</tr>
<tr>
<td>APTT (sec)(normal 26-36)</td>
<td>35.6</td>
<td>46.2</td>
<td>3.1</td>
<td>25.5-64.9</td>
</tr>
<tr>
<td>ATIII (%) (normal 80-120)</td>
<td>85</td>
<td>47.6</td>
<td>5.0</td>
<td>27-77</td>
</tr>
</tbody>
</table>

SEM, standard error of the mean; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; DO₂, oxygen delivery; VO₂, oxygen consumption; Max, maximum; AaGradient, alveolar arterial oxygen difference; PT, prothrombin time; APTT, activated partial thromboplastin time; ATIII, antithrombin III.

Table 3 Hemodynamic, respiratory and coagulation variables.

Linear regression analysis showed significant correlations between maximum TNF-α levels and systemic vascular resistance (p < 0.02, r=0.70), cardiac index (p < 0.02, r=0.72), volume of fluid
infused in the operating room (p < 0.02, r=0.69) and in the ICU (p<0.02, r=0.80) and maximum infusion rate of dopamine (p < 0.02, r=0.69).

Respiratory System
Twenty patients remained intubated for less than 24 hrs, 3 for 24-48 hrs and 2 patients required prolonged ventilatory support (14 and 21 days). Respiratory variables are summarized in Table 3. There was a significant correlation between maximum TNF-α level and the Lung Injury Score (p < 0.02, r=0.64).

Renal Function
One patient developed multiple organ failure and required continuous venovenous hemodialysis for 16 days. The remaining 24 patients showed no significant change in creatinine clearance from preoperative values. The patient who developed multiple organ failure had the highest top level of TNF-α recorded in this study: 83.000 ng/L.

Coagulation Parameters
Coagulation parameters are summarized in Table 3. Values for thrombocyte count were available for 24 patients, fibrinogen levels for 16 patients, prothrombin time and activated partial thromboplastin times for 15 patients, and antithrombin III levels in 14 patients. There were significant correlations between maximum TNF-α level and prothrombin time (p < 0.02, r=0.79) and activated partial thromboplastin time (p < 0.05, r=0.72) but not with fibrinogen and antithrombin III levels.

Discussion
Isolated limb perfusion with r-TNF-α, melphalan and r-IFN-γ produced a severe but short-lived systemic reaction characterized by high fever, high cardiac output, low peripheral resistance, activated clotting and an increased A-a gradient for oxygen. All patients required either fluid resuscitation or dopamine infusion or both to maintain adequate blood pressure. The clinical picture resembled septic shock and adult respiratory distress syndrome, lasting for about 24 hours. Since, in 4 other patients, perfusion with only melphalan (without r-TNF-α and r-IFN-γ) did not trigger a rise in systemic TNF-α levels, and extremely high levels of TNF-α were measured in the systemic circulation of the patients described here, both during and shortly after perfusion, leakage of r-TNF-α from the perfusion system into the systemic circulation is likely to be the explanation for the sepsis-like state that was observed. Washout of remnant r-TNF-α once the circulation was restored may have contributed to the high systemic TNF-α levels. The observed leakage of 131I labeled albumin from the perfusion system, which ranged between 0 and 8% (median 2%) supports the role of TNF-α leakage as the primary cause of the postoperative events described earlier. The extent of leakage is similar to that reported in the literature [23]. Moreover, it is known from animal experiments, that administration of r-TNF-α leads to tissue injury and metabolic derangements similar to those seen in septic shock [24]. In theory, systemic TNF-α levels in these patients may also have been raised by the systemic response to extracorporeal circulation, hyperthermia, and the presence of indwelling plastic cannulae [25 -27]. Tissue damage induced by the combined effects of heat, melphalan and r-TNF-α was also considerable in all cases and this in itself could have contributed to an increase in TNF-α levels and signs of systemic inflammatory response. However, we feel that the TNF-α levels we measured were too high to be explained by
endogenous production of this cytokine. Maximum systemic TNF-α levels (median 25409 ng/L, range 2284-83000) were several orders of magnitude higher than TNF-α levels previously reported in other forms of shock. In a series of 79 patients with meningococcal disease and/or septicemia all patients with TNF-α levels over 100 ng/L died [28]. In septic shock median TNF-α levels of 120 ng/L have been reported [11]. In our patients TNF-α levels were very high initially but fell rapidly: 12 hours postperfusion TNF-α levels had returned to baseline values. In view of their high TNF-α levels recovery in our patients was remarkably rapid: 80% could be transferred from the ICU the day following perfusion. How can this discrepancy between TNF-α levels and clinical course be explained?

Theoretically the measured systemic TNF-α levels could represent an inactive form of the polypeptide. Since the preparation was tested in a bioassay by the manufacturer it is unlikely that r-TNF-α was administered to the patients in an inactive form. It has recently been shown that TNF-α binds to two different types of receptors, one of them 55 kilodalton in size, the other 75 kilodalton. The extracellular portions of these receptors, TNF-α binding protein type 1 and 2 respectively, can become separated from the cell membrane by proteolysis, and can bind and inactivate TNF-α in the circulation. In theory, rapid and extensive binding of r-TNF-α to these soluble receptors could therefore explain the relatively mild clinical course in our patient group. In our study only total TNF-α was measured. Because of these limitations the question whether the high TNF-α levels represent unbound, active TNF-α cannot be answered. Future studies should determine both unbound TNF-α and TNF-α soluble receptor complexes. TNF-α in our series was not cleared fast; the mean half-life of 80 minutes in our patients is considerably longer than the 10 - 15 minutes reported in the literature. It has been suggested that patients with cancer are chronically exposed to increased levels of endogenous TNF-α and so may have increased tolerance to the effects of TNF-α [29]. The patients in this study received r-IFN-γ subcutaneously for 2 days preoperatively to sensitize them to the effects of TNF-α. In animals this is highly effective [30]. It is not unreasonable to assume that any downregulation of receptors in our patients was probably negated by the effects of r-IFN-γ pretreatment. Moreover, baseline values of plasma TNF-α were several orders of magnitude lower than maximum TNF-α levels so any pre-existing tolerance probably had insignificant effects on the subsequent clinical course. Pinsky and coworkers have shown that the persistence of TNF-α and IL-6 levels rather than peak levels of cytokines predicts a poor outcome in patients with septic shock [31]. Accordingly, it is possible that the rapid decline in TNF-α levels and the lack of a repetitive stimulus for TNF-α release was the reason that our patients recovered so quickly with no deaths in this series.

Finally it should be borne in mind that much of the injury induced by TNF-α results from local production of the protein and its subsequent action at short range. Systemic levels of this cytokine only weakly reflect what is going on at the local level. Low levels in the circulation do not exclude high levels of TNF-α in the tissues and, inversely, high systemic levels do not necessarily reflect high concentrations in the tissues of the patient.

As far as management of these patients in the ICU is concerned, hypotension was the key problem and the presence of a Swan-Ganz catheter proved to be very valuable in its treatment. Colloids and crystalloids were infused to a pulmonary wedge pressure of 12 mmHg. However, large infusions of volume (mean of 10 L within the first 24 h) did not correct the hypotension in the majority of patients. Accordingly 24 out of 25 patients were treated with intermediate dose dopamine infusions (mean 5 µg/kg/min). The patient with the highest TNF-α level also needed norepinephrine to maintain adequate blood pressure but this could not prevent the development of renal failure. Dopamine could usually be stopped the day following admission to the ICU and the Swan-Ganz catheter was removed a few hours
later. All patients but one retained good renal function. A large spontaneous diuresis followed the resolve of the sepsis syndrome on day 2. Patients were ventilated in a pressure support mode as soon as their ventilatory drive was restored following anesthesia. Signs of Adult Respiratory Distress Syndrome were usually discrete and only two patients needed high levels of positive end-expiratory pressure or inspiratory oxygen concentration to maintain adequate saturation. These two patients required mechanical ventilation for almost three weeks. Successful extubation was performed in 21 out of 25 patients within 24 hours. Clinically relevant coagulopathy was not observed in any patient. There is little doubt that patients undergoing isolated limb perfusion with r-TNF-α will benefit from postoperative care in an ICU. Data derived from a Swan-Ganz pulmonary artery catheter are helpful to direct fluid administration and treatment with inotropes. Preferably a pulmonary artery catheter is introduced before the perfusion is started.

In conclusion this study shows that isolated limb perfusion with r-TNF-α leads to very high systemic TNF-α levels and transient serious signs of sepsis, pulmonary dysfunction and activated clotting, probably due to leakage of r-TNF-α from the perfusate. Despite high systemic TNF-α levels recovery in most cases is rapid and complete.

References


