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High incidence of coagulopathy in phase II studies of recombinant tumor necrosis factor in advanced pancreatic and gastric cancers

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This multi-center trial was carried out to assess the therapeutic potential of recombinant tumor necrosis factor (rTNF) as the first form of systemic therapy for advanced carcinomas of gastric and pancreatic origin. To be eligible patients were required to have no overt sign of coagulopathy and hepatic function studies with enzymes less than two times beyond the normal range. Twenty nine patients with gastric cancer and 26 with pancreatic cancer were entered from various institutions in the Southwest Oncology Group with 27 and 22, respectively, meeting eligibility criteria. Drug treatment consisted of rTNF (Genentech) given at a dose of 150 μg intravenously for five consecutive days every 3 weeks; 50% dose reduction was made for acute intolerance such as hypotension or severe fever and chills. Although eight patients with gastric cancer and five patients with pancreatic cancer received four or more courses of treatment, no objective antitumor responses were recorded. As in other trials common toxicities of rTNF included nausea and vomiting, chills and fever, hypotension, headache, myalgias, fatigue and malaise. However, in this trial, other toxicities became prominent: four episodes of symptomatic disseminated intravascular clotting occurred among patients with pancreatic cancer. Eleven with this disease and five with gastric cancer manifested laboratory findings of abnormal amounts of fibrin split products, and/or hypofibrinogenemia, and/or thrombocytopenia after treatment began. Other laboratory abnormalities that were commonly encountered included hyperglycemia, hypertriglyceridemia, anemia, neutropenia and an elevation in liver enzymes. We conclude that rTNF does not demonstrate antitumor efficacy against adenocarcinomas of the stomach and the pancreas. Moreover, rTNF's action in activating the coagulation system and other metabolic effects pose a hazard to patients with adenocarcinoma that may be particularly prone to manifest these changes as part of their illness.

Key words: Coagulopathy, gastric cancer, pancreatic cancer, phase II study, recombinant tumor necrosis factor.

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Introduction

Tumor necrosis factor (TNF) was defined by Old and collaborators as the antitumor activity found in the serum of animals treated with endotoxin after priming with immunomodulators such as Bacillus Calmette-Guérin (BCG) or *Clostridium parvum*.[1–3] Accurate assessment of the therapeutic potential of

TNF would await the availability of large quantities of homogeneously purified recombinant material (rTNF) produced by recombinant DNA methodologies.[4,5] With this material, antitumor effects were demonstrated against human tumor cell lines[6] and xenografts in nude mice.[7] Synergy with other cytokines such as interferon-γ (IFN-γ) has been subsequently shown.[7–9] In addition, enhanced antitumor effects have been noted in combination with a wide variety of chemotherapeutic agents[10,11] but particularly topoisomerase II-interacting drugs such as etoposide.[11] Postulated cytotoxic mechanisms include the binding to a cell surface receptor, followed by internalization and lysis of the target cell via release of lysozomal enzymes.[12,13] Indirect cytotoxicity via endothelial damage has also been postulated.[14] In fact, prominent effects on endothelial cells[14–18] and on the coagulation pathways[19,20] have been identified; and an increasing number of anti-infective[12,21,22] and metabolic effects[12,23–25] studied in the laboratory may have clinical consequences.

Phase I trials utilizing rTNF by itself in various schedules and routes of administration universally resulted in fever and chills, which were dose-dependent. Other common toxicities included diarrhea, fatigue, headache and inflammation at the local injection site. Laboratory abnormalities included mild to moderate anemia and hypertriglyceridemia, with sporadic leukopenia and hepatic transaminase elevations.[25–29] At doses exceeding 200 $\mu g/m^2$, mild hypotension was also observed. A dose of rTNF of 150 $\mu g/m^2$ daily $\times 5$ administered intravenously (i.v.) was deemed the maximum tolerated dose (MTD) for phase II trials by the Mayo Clinic.[28] Hypotension was noted to occur primarily on day 1 and responded to i.v. fluids. Subjective intolerance was improved by i.v. meperidine. On the basis of this experience, and the desirability to seek agents with antitumor activity against pancreatic and gastric cancers, the Southwest Oncology Group (SWOG) initiated simultaneous phase II studies with rTNF at this schedule's MTD (studies SWOG 8755 and 8760). Both these studies opened for patient entry in June 1988, and were closed in January 1990, with results partly summarized in an abstract[30] and in a brief report of study 8755.[31] Studies by SWOG of rTNF in colon cancer, bladder cancers, leukemia and multiple myeloma await final analysis and publication. The high incidence of coagulopathy noted in both these studies has prompted us to report in detail this experience and review likely pathogenic mechanisms.

Patients and methods

Patient eligibility was similar in both protocols (Table 1), and required bidimensionally measurable disease and performance status of 2 or better (SWOG scale; Karnofsky 50–100). This was to be the first systemic therapy for the patient and the interval from radiation or surgery had to exceed 4 or 2 weeks, respectively. Because of the potential toxicities of rTNF, any cardiac disease, bleeding or thromboembolic diathesis, lymphagitic spread were specifically excluded. All patients required in addition to adequate bone marrow (granulocytes $>1500/\mu l$, platelets $>100\,000/\mu l$), renal (creatinine <1.5 mg/100ml) and hepatic function (bilirubin <1.5 mg/100ml and SGOT <2 times normal or <5 times if due to tumor), baseline coagulation tests (PT, PTT, thrombin time, fibrinogen and fibrin split products) and cardiopulmonary status (EKG and FEV_1). Patients with abnormalities exceeding their institution's normal ranges in coagulation parameters were excluded.

The treatment plan consisted of rTNF daily for 5 days every other week as long as progression of disease or intolerable toxicities did not occur. The drug was prepared by Genentech, Inc. (South San Francisco, CA, USA) via recombinant DNA technology, and purified to greater than 99% with a specific activity of approximately 4×10^7 U/mg of protein as defined in the L929 cytotoxicity assay and less than 1.0 ng/mg of protein of endotoxin. Each vial containing 0.5 mg/ml was diluted to a

Table 1. Patient eligibility for SWOG 8760 (gastric) AND 8755 (pancreatic)

Histologic confirmation of adenocarcinoma
Bidimensionally measurable disease
Age 18 or more
Life expectancy 3 months or greater and SWOG performance status of 2 or better
No prior cytotoxic chemotherapy
Completed all therapy 3 weeks or longer
White cell count $>4000/\mu l$ and absolute granulocyte count >1500
Platelet count $>100\,000/\mu l$; prothrombin <14 s
Partial thromboplastin time <34 s; thrombin time <2 s
Fibrinogen >200 mg/dl; fibrin split products <40 μg/ml
Serum creatinine ≤ 2.0 mg/dl; proteinuria not exceeding 2+
Bilirubin <1.5 mg/dl, enzymes $<2\times$ normal values
FEV_1 70% predicted or better; EKG normal and/or no serious cardiac disease
Signed informed consent

concentration of 0.05 mg/ml with normal saline to be used within 4 h, and further mixed with human serum albumin at a concentration of 2 mg/ml to avoid adherence of rTNF to the infusion apparatus. The initial dose administered was 150 $\mu g/m^2$ i.v. Dose modifications to 75 $\mu g/m^2$ were prescribed for any grade 2 or greater toxicities, except if these consisted of hypotension, cardiac or central neurologic changes, which required consultation with the study coordinator before resumption. Pretreatment with meperidine (50 mg) and acetominophen (500–1000 mg) were strongly recommended and usually repeated once after administration of rTNF.

Follow-up studies included day 3 and 5 hemograms during every treatment week, and additional chemistries and coagulopathy screen on day 5 of every treatment week. Tumor measurements were repeated every 8 weeks. The graded toxicity scale with the common toxicity criteria adopted by the Cancer Therapy Evaluation Program of the National Cancer Institute and by the Southwest Oncology Group was employed to assess toxicities, and standard criteria of response and endpoint definitions were applied. Grading of fatigue, malaise and rigors specific for these protocols were also implemented: grade 1 if there was no interference with activity, grade 2 if it required bed rest but not exceeding 50% of the day, grade 3 if it exceeded 50% and grade 4 if the patient became unable to care for self. Studies were opened for patient entry by all institutions of the Southwest Oncology Group once approved by individual institutional review boards. Patients signed forms of informed consent prior to entry.

Results

A total of 29 patients with gastric cancer and 26 patients with pancreatic cancer were registered. Four patients on 8755 (pancreatic) and two on 8760 (gastric) were disqualified because they did not meet eligibility criteria of measurability (one patient) or laboratory data including abnormal EKG or fibrin split products (four patients) or initiated treatment beyond the specified limits (one patient). The remainder of the patients were evaluable for toxicity and for therapeutic effects. Patient characteristics and number of treatment courses are listed in Table 2. A male predominance is observed in both disease sites; gastric cancer patients were slightly younger (median 58 versus 61 years for pancreatic cancer).

Table 2. Patient characteristics and treatment courses (eligible patients)

	Gastric	Pancreatic
Men (M)	20	15
Women (W)	7	7
Median age in years (range)	58 (23–77)	61 (44–70)
Number of courses (M/W)		
1	7/3	7/0
2	4/2	2/1
3	2/1	3/4
4	3/1	2/1
>4	4/0	1/1
	(5,7,8,13)	(15,5)
Performance status		
0	14	1
1	12	19
2	1	2

Toxicity

Table 3 indicates the frequency of toxicities observed among the two groups of patients. These are roughly comparable and moderately severe; coagulopathies and symptomatic thromboembolic events were more severe and frequent, however, among patients with carcinoma of the pancreas. Pulmonary emboli were documented in one patient and deep vein thrombosis of the lower extremity in another, both occurring within the first three cycles of therapy. One patient had peripheral digital gangrene, and another had marantic endocarditis and colon perforation after three cycles. These four patients and seven others with carcinoma of the pancreas manifested laboratory abnormalities of disseminated intravascular coagulation (fibrin split products >40 $\mu g/ml$). Five patients with gastric cancer also showed such changes. Hypotension was

Table 3. Common toxic events (higher than grade 2 in severity)

	Gastric ($n = 27$)	Pancreatic ($n = 22$)
Nausea/vomiting	18	16 (3)
Chills/fever	22 (2)	20 (2)
Hypotension	7 (1)	14 (1)
Flu-like symptoms	12	14
Headache	6	7 (1)
Diarrhea	4	5
Constipation	4	3
Bleeding	3	1
Thromboembolism	—	4 (4)

Table 4. Laboratory changes (higher than grade 2 in severity)

	Gastric ($n = 27$)	Pancreatic ($n = 22$)
Hyperglycemia	16	15 (1)
Anemia	12 (3)	14 (2)
Liver enzymes	11 (4)	14 (1)
Liver bilirubin	1	4 (2)
Hypertriglyceridemia	18	9
Coagulopathy[a]	5	11 (4)
Neutropenia	8 (2)	5
Thrombocytopenia	1	4 (1)
Proteinuria	1	4

[a] See text.

frequent during the first cycle of therapy and appeared to be more common among males, prompting cessation of therapy in some instances. Nevertheless, eight patients with gastric cancer received four or more cycles, with one receiving 13 cycles until progression of disease.

Laboratory findings related to treatment are shown in Table 4. Hyperglycemia was frequent among both groups, whereas hypertriglyceridemia was more frequently found among gastric cancer patients. Liver enzymes, while frequently abnormal prior to treatment, became more abnormal in 14 and 11 patients, respectively. The alkaline phosphatase in several patients also became transiently elevated. In patients receiving several cycles, the abnormalities frequently reverted towards normal after initial elevations during the first two cycles. Hepatic involvement by tumor was very common but fluctuations in the enzymes indicated a probable relationship to the rTNF treatment.

Therapeutic effects

No complete or partial responses were observed in either group among the 27 gastric and 22 pancreatic cancer patients meeting eligibility criteria, the 95% confidence intervals for response rate in the two sites are 0% to 13%, and 0% to 15%, respectively. Eight patients with gastric cancer received four or more cycles, and were stable for periods varying from 6 to 39 weeks, before manifesting progression; all but one were men. Both men and women were represented among patients with pancreatic cancer receiving four or more cycles (Table 2). Crossover to cytotoxic chemotherapy once going off study was attempted in some patients, but no responses were documented. Figure 1 depicts the survival of both groups and indicates a shorter median survival for pancreatic (3.1 months) than for gastric cancer patients (6.0 months).

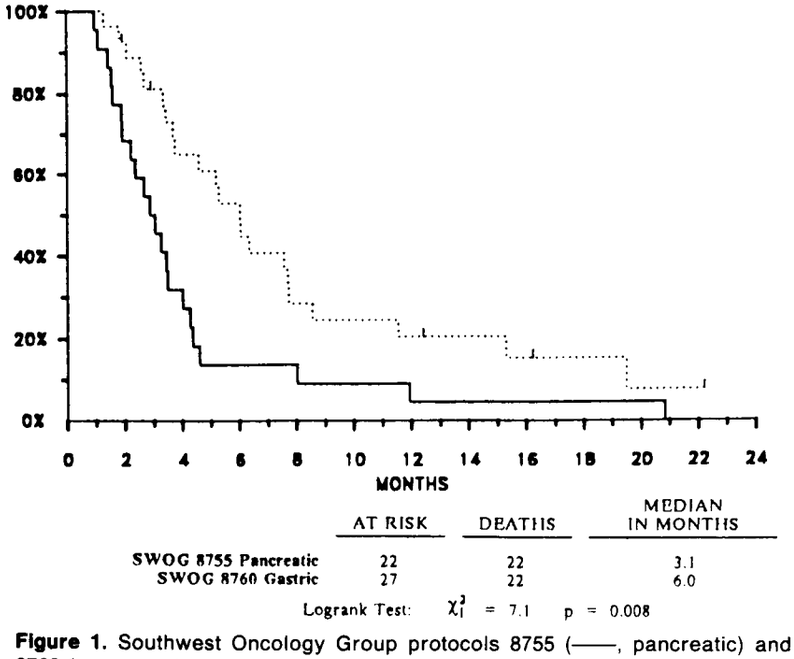

Figure 1. Southwest Oncology Group protocols 8755 (——, pancreatic) and 8760 (·····, gastric).

Discussion

The therapeutic results with rTNF in disease-oriented phase II studies have not been encouraging to date.[30–33] Nevertheless, the clinical studies of rTNF have continued to explore antitumor effects with other cytokines[34] and there is interest in evaluating combinations with chemotherapeutic agents. The current experience, however, indicates that considerable caution must be exercised when administering these agents to patients with these gastrointestinal malignancies. In particular, patients with carcinoma of the pancreas were prone to severe coagulopathies; both groups also experienced a gamut of toxicities accompanied by frequent laboratory abnormalities such as hypertriglyceridemia and hyperglycemia. Also, noteworthy among male patients was the presence of hypotension during the first course.

Coagulopathy in relation to TNF therapy has not been consistently emphasized by the previous clinical studies in cancer patients. In fact, one abstract suggests rTNF administration is not associated with any problems related to activation of the coagulation system.[35] In a phase I study painful erythema at the site of administration was dose-limiting in one patient receiving 150 $\mu g/m^2$/day and in two patients receiving 200 $\mu g/m^2$/day.[26] No evidence of disseminated intravascular coagulation was noted, but 16 of 19 patients had decreases in platelet counts and most had consistent increases in triglycerides.[26] Severe phlebitis of the upper extremity was noted after the third cycle in a patient with rectal adenocarcinoma who received 200 $\mu g/m^2$/day × 5 days.[28] This study also reported eosinophilia and hypertriglyceridemia, but thrombocytopenia in only one patient.[28] Another detailed phase I study dosing rTNF every 72 h provided a detailed analysis of effects on platelets, granulocytes and lymphocyte counts. Statistically significant decreases in lymphocytes and platelets were observed; the latter was clinically unimportant and no thromboembolic event was recorded.[29] A phase I study giving rTNF by continuous infusion showed lowering of platelets, increases in triglycerides and lowering of high density lipoproteins.[27] Several abnormalities involving the coagulation system (Fi_{1+2}, protein C activation peptide and fibrin peptide A) were documented in 12 patients receiving more than 3 × 10 $\mu g/m^2$/24 h but not in the 11 patients receiving lesser doses.[36] In phase II studies, one definite thrombotic episode requiring anticoagulants has been noted in a companion study among 21 patients with colorectal study by the same dose schedule (E Hersh, unpublished).[37] Another study in patients with colorectal cancer by a different dose schedule (100 $\mu g/m^2$ twice daily for 5 days) reported two patients with retinal vein thrombosis.[32] This experience and ours suggests that contrary to phase I studies that may have included patients less prone to coagulopathy there may be a hazard to rTNF administration in some patients. Also, the doses received by most patients in the phase I studies were lower than 150 $\mu g/m^2$. In combination with IFN-γ subclinical intravascular coagulation changes were noted at lower doses of rTNF, suggesting a synergistic effect *in vivo*.[34]

It is conjectural whether many of the abnormalities recorded were actually disease-related changes that were aggravated by the administration of rTNF. However, recent studies point to rTNF as a potent initiator of coagulation in normal subjects as well.[20] When rTNF was administered to six healthy men at a dose of 50 $\mu g/m^2$, within 45 min one could document a significant increase in activated factor X formation and the activation of prothrombin with fragment Fi_{1+2} showing a sustained increase with highest levels by 4–5 h. However, the intrinsic coagulation pathway was not activated. Also, there were no changes in platelets observed, which differs from the above observations in cancer patients. These coagulation changes are believed to occur via mechanisms which are similar to those triggered by sepsis. Another study, in fact, implicates TNF in coagulation changes following endotoxin administration to normal volunteers.[36,38,39] Tissue plasminogen activator release by endotoxin is followed by a more sustained release of plasminogen-activator inhibitor-1 which is likely mediated by TNF. This inhibitor has been shown to increase after continuous i.v. TNF infusion and to be released into malignant ascites after intraperitoneal treatment.[40,41] Thus both activation of the coagulation system and fibronolysis may be expected after TNF. Paradoxically, IFN-γ has been shown to block some of the actions of TNF leading to induction of urokinase plasminogen activation.[42]

In our study we excluded patients with laboratory or clinical evidence of coagulopathy prior to treatment. Nevertheless, these abnormalities became manifest in half the patients with pancreatic cancer as well as in some patients with gastric cancer. Although thromboembolic events commonly complicate the course of these adenocarcinomas, one must strongly raise the possibility that coagulopathies are further triggered by rTNF.

In conclusion, our results indicate no antitumor activity for rTNF in patients with advanced adenocarcinomas of the stomach and pancreas in a daily ×5 schedule. Moreover, we caution that the use of this cytokine in a patient population with a high incidence of preexisting coagulopathy may be hazardous. Finally, these findings fuel speculations that TNF's procoagulant actions play a role in the thromboembolic complications associated with these adenocarcinomas.

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References

1. Carswell EA, Old LJ, Kassel RL, *et al.* An endotoxin-induced serum factor that causes necrosis of tumors. *Proc Natl Acad Sci USA* 1975; **72**: 3666–70.
2. Helson L, Green S, Carswell EA, *et al.* Effect of tumor necrosis factor on cultured human melanoma cells. *Nature* 1975; **258**: 731–2.
3. Oettgen HF, Carswell EA, Kassel RL, *et al.* Endotoxin-induced tumor necrosis factor. *Recent Results Cancer Res* 1980; **75**: 207–12.
4. Pennica D, Nedwin GE, Hayflick JS, *et al.* Human tumor necrosis factor: precursor structure expression and homology to lymphotoxin. *Nature* 1984; **312**: 724–8.
5. Gray PW, Aggarwal BB, Benton CV, *et al.* Cloning and expression of cDNA for human lymphotoxin, a lymphokine with tumor necrosis activity. *Nature* 1984; **312**: 712–4.
6. Rosenblum MG, Donato NJ, Gutterman JU. Characterization of recombinant tumour necrosis factor-alpha; antiproliferative effects on human cells in culture. *Lymphokine Res* 1988; **7**: 107–17.
7. Balkwill F, Lee A, Aldan G, *et al.* Human tumour xenografts treated with recombinant human tumour necrosis factor alone or in combination with interferons. *Cancer Res* 1986; **46**: 3990–3.
8. Stone-Wolff DS, Yip YK, Kelker HC. Interrelationships of human interferon-gamma with lymphotoxin and monocyte cytotoxin. *J Exp Med* 1984; **159**: 828–43.
9. Williamson BD, Carswell EA, Rubin BY, *et al.* Human tumor necrosis factor produced by human B-cell lines: synergistic cytotoxic interaction with human interferon. *Proc Natl Acad Sci USA* 1983; **80**: 5397–401.
10. Regenass U, Muller M, Cursebellas E, *et al.* Antitumor effects of tumor necrosis factor in combination with chemotherapeutic agents. *Int J Cancer* 1987; **39**: 266–73.
11. Alexander RB, Nelson WG, Coffey DS. Synergistic enhancement by tumor necrosis factor of an *in vitro* cytotoxicity from chemotherapeutic drugs targeted at DNA topoisomerase II. *Cancer Res* 1987; **47**: 2403–6.
12. Tracey KJ, Vlassara H, Cerami A. Cachectin/tumour necrosis factor. *Lancet* 1989; **i**: 1122–6.
13. Tsujimoto M, Vilcek J. Tumor necrosis factor receptor in HeLa cells and their regulation by interferon-gamma. *J Biol Chem* 1986; **261**: 5384–5388.
14. Shimomura K, Manda T, Mukumoto S, *et al.* Recombinant human tumor necrosis factor-alpha: thrombus formation is a cause of antitumor activity. *Int J Cancer* 1986; **41**: 243–7.
15. Bevilacqua MP, Pober JS, Majeau GR, *et al.* Recombinant tumor necrosis factor induces procoagulant activity in cultures human vascular endothelium: characterization and comparison with the actions of interleukin 1. *Proc Natl Acad Sci USA* 1986; **83**: 4533–7.
16. Conway EM, Bach R, Rosenberg RD, *et al.* Tumor necrosis factor enhances the expression of tissue factor mRNA in endothelial cells. *Thromb Res* 1989; **53**: 231–41.
17. Nawroth PP, Stern DM. Modulation of endothelial cell hemostatic properties by tumor necrosis factor. *J Exp Med* 1986; **163**: 740–3.
18. van Hinsbergh VW, Koistra T, van den Berg EA, *et al.* Tumor necrosis factor increases the production of plasminogen activator inhibitor in human endothelial cells *in vitro* and in rats *in vivo*. *Blood* 1988; **72**: 1467–73.
19. Moore KL, Esmon CT, Esmon NL. Tumor necrosis factor leads to internalization and degradation of thrombomodulin from the surface of bovine aortic endothelial cells in culture. *Blood* 1989; **73**: 159–65.
20. van der Poll T, Buller HR, ten Cate H, *et al.* Activation of coagulation after administration of tumor necrosis factor to normal subjects. *N Eng J Med* 1990; **322**: 1622–7.
21. Girardin E, Grau GE, Drayer J-M, *et al.* Tumor necrosis factor and interleukin-1 in the serum of children with severe infectious purpura. *N Eng J Med* 1988; **319**: 397–400.
22. Haldaris CG, Haynes JD, Meltzer MS, *et al.* Serum containing tumor necrosis factor is cytotoxic for the human malaria parasite *Plasmodium falciparum*. *Infect Immunol* 1983; **42**: 385–93.
23. Sassa S, Kawakami M, Cerami A, *et al.* Inhibition of the growth and differentiation of erythroid precursor cells by an endotoxin-induced mediator from peritoneal macrophages. *Proc Natl Acad Sci USA* 1983; **80**: 1717–90.
24. Pekala PH, Kawakami M, Angus CW, *et al.* Selective inhibition of synthesis of enzymes for *de novo* fatty acid biosynthesis by an endotoxin-induced mediator from exudate cells. *Proc Natl Acad Sci USA* 1983; **80**: 2743–7.
25. Warren RS, Starnes HJ Jr, Gabrilove JL. The acute metabolic effects of tumor necrosis factor administration in humans. *Arch Surg* 1987; **122**: 1396–400.
26. Jakubowski AA, Casper ES, Gabrilove JL, *et al.* Phase I trial of intramuscularly administered tumor necrosis factor in patients with advanced cancer. *J Clin Oncol* 1989; **7**: 298–303.
27. Sherman ML, Spriggs DL, Arthur KA, *et al.* Recombinant human tumor necrosis factor administered as a 5-day continuous infusion in cancer patients: Phase I toxicity and effects on lipid metabolism. *J Clin Oncol* 1988; **6**: 344–50.
28. Creagan ET, Kovach JS, Moertel CG, *et al.* A phase I trial of recombinant human tumor necrosis factor. *Cancer* 1988; **62**: 2467–71.
29. Blick MB, Sherwing SA, Rosenblum M, *et al.* A Phase I study of recombinant tumor necrosis factor in cancer patients. *Cancer Res* 1987; **7**: 2986–9.
30. Muggia F, Brown T, Goodman P, *et al.* Recombinant tumor necrosis factor (rTNF) intolerance in pancreatic and

gastric cancers: Southwest Oncology Group (SWOG) trials. *Proc Am Ass Cancer Res* 1990; **31**: 185 (abstract 1102).
31. Brown TD, Hersh EM, Goodman PJ, *et al.* A Phase II trial of recombinant tumor necrosis factor (rTNF) in patients with adenocarcinoma of the pancreas: a Southwest Oncology Group Study. *J Biol Resp Modifiers*, in press.
32. Kemeny N, Childs B, Larchian W. A Phase II trial of recombinant tumor necrosis factor in patients with advanced colorectal carcinoma. *Cancer* 1990; **66**: 659–63.
33. Hardy J, Jones ME, Gore C, *et al.* Treatment of advanced ovarian cancer with intraperitoneal tumour necrosis factor. *Eur J Cancer* 1990; **26**: 771.
34. Demetri GD, Spriggs DR, Sherman ML, *et al.* A phase I trial of recombinant human tumor necrosis factor and interferon-gamma: effects of combination cytokine administration *in vivo*. *J Clin Oncol* 1989; **7**: 1545–53.
35. Kempin S, Gold P, Glaser B, *et al.* Hemostatic alterations in patients receiving recombinant tumor necrosis factor. *Blood* 1986; **68**: 335 (abstract).
36. Bauer KA, tenCate H, Barzegar S, *et al.* Tumor necrosis factor infusions have a procoagulant effect on the hemostatic mechanism of humans. *Blood* 1989; **74**: 165–72.
37. Hersh EM, Metch BS, Muggia FM, *et al.* Phase II studies of recombinant human tumor necrosis factor alpha in patients with malignant disease: a summary of the Southwest Oncology Group experience. *J Immunother* 1991; **10**: 426–31.
38. Van Deventer SJH, Buller HR, tenCate SW, *et al.* Experimental endotoxemia in humans: analysis of cytokine release and coagulation, fibrinolytic and complement pathways. *Blood* 1990; **76**: 2520–6.
39. Suffredini AF, Harpel PC, Parillo JE. Promotion and subsequent inhibition of plasminogen activation after administration of intravenous endotoxin to normal subjects. *N Eng J Med* 1989; **320**: 1165–73.
40. Van Hinsbergh VWM, Bauer KA, Koorstrat, *et al.* Progress of fibrinolysis during tumor necrosis factor infusion in humans. Concomitant increase in tissue-type plasminogen activator, plasminogen activator inhibitor Type-1 and Fibrin (ogen) degradation products. *Blood* 1990; **76**: 2284–9.
41. Markert C, Kaufman M, Raeth U, *et al.* rhuTNF-induced increase in PAI-1 in malignant ascites of tumor patients. *Proc Am Ass Cancer Res* 1991; **32**: 193 (abstract 1150).
42. Nichbala MJ, Picarella MS. Tumor necrosis factor induction of endothelial urokinase-type plasminogen activator mediated proteolysis of extracellular matrix and its antagonism by β-interferon. *Blood* 1992; **79**: 678–87.

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