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Phase I clinical trial of recombinant human tumor necrosis factor

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Summary. A phase I and pharmacokinetic study of recombinant tumor necrosis factor (rH-TNF Asahi) was carried out in 29 patients, who received a total of 72 courses with doses ranging from 1 to 48×10^4 units/m^2. Drug was given as 1-h i. v. infusions. Acute toxicities, taking the form of fever, chills, tachycardia, hypertension, peripheral cyanosis, nausea and vomiting, headache, chest tightness, low back pain, diarrhea and shortness of breath, were seen, but were not dose-limiting or dose-related. Some early rise in SGOT, without any change in serum bilirubin, was noted at the highest doses. Eosinophilia, monocytosis, mild hypocalcemia and an increase in fibrin degradation products were seen in a few patients. The dose-limiting toxicity was hypotension, which occurred after the end of the drug infusion and was seen in all 5 patients treated at the highest dose. There was no mortality or long-term morbidity. There were no responses. Pharmacokinetic studies indicated a rapid plasma clearance and a short plasma half-life, generally less than 0.5 h.

Introduction

Carswell et al. [2] were the first to report that mice which had been primed with BCG and then challenged with endotoxin, produced, in their serum, a factor which could cause tumor necrosis in other animals. This was termed tumor necrosis factor (TNF). Recently, the gene encoding for human TNF has been cloned and expressed in *E. coli* [10]. This material, which is a non-glycosylated protein with a molecular weight of 17000 daltons, has been evaluated for antitumor activity in vitro and in vivo. Of 26 human tumor cell lines tested, 5 (neuroblastoma SYM-1, lung cancer PC-10, breast cancer BT-20, myosarcoma KYM-1, and monocytic leukemia THP-1) showed a high degree of sensitivity, with an IC_{50} of less than 1 unit/ml [5]. In in vivo studies it produced cures against the meth-A sarcoma and the colon 26 carcinoma, but not against the B16 melanoma, when given i. v. [5].

On the basis of high and selective antitumor activity in animals, this compound was advanced to phase I clinical trial in August 1985, under an IND from the Bureau of Biologics of the Food and Drug Administration.

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Materials and methods

The drug was supplied by the Asahi Chemical Industry Company Limited, Tokyo, Japan, in vials containing 5×10^5 or 5×10^4 units. The material was better than 99% pure after purification by ion exchange chromatography, gel filtration and affinity chromatography. It contained no detectable endotoxin or DNA. The material was assayed by cytotoxicity against L-M cells. The activity in units per milliliter is defined as the reciprocal of the dilution resulting in 50% cell survival. The specific activity of the material was 2.2×10^6 units/mg. Patients with advanced cancer not amenable to other treatments, or for whom other treatments had proven ineffective, were entered on the study after giving written informed consent. The requirements for entry into the study were an age of 15–70 years, an expected survival of at least 2 months, a performance status of ≤ 2 (Eastern Cooperative Oncology Group; ECOG), at least a 3-week interval since the last dose of potentially myelosuppressive therapy (6 weeks for a nitrosourea and mitomycin C) and recovery from reversible toxicity, a 2-week interval since radiation therapy or surgery (except for minor procedures), and the absence of acute intercurrent complications, pregnancy, or a history of asthma. The minimum hematologic parameters required were a white cell count of 4000/mm^3 and a platelet count of 100000/mm^3. The minimum biochemical parameters required were SGOT ≤ 100 IU/l, and serum bilirubin and serum creatinine ≤ 2 mg/dl.

The observations recorded and their frequency were as follows: temperature, pulse and blood pressure every 2 h for 12 h and then every 4 h until they returned to baseline; complete blood count, differential count, platelet count, serum chemistries (Na^+, K^+, Ca^{2+} and PO_4^{3-}, creatinine, uric acid, total protein, albumin, bilirubin, alkaline phosphatase, LDH, SGOT and BUN) at 24, 48 and where possible at 72 h after drug infusion and then weekly for 3 weeks; prothrombin time, partial thromboplastin time, serum fibrinogen, fibrin degradation products and fibrin monomer at 48 h and then weekly for 3 weeks; EKG at 24 h after treatment.

All patients were hospitalized from the day before treatment to 48 h after treatment. On the day before treatment blood was drawn for antibodies to TNF. One hour before drug infusion, 0.025 ml of the solution to be injected was injected i. d. to exclude patients with allergy to the rH-TNF. Patients were pretreated with 50 mg indometha-

Table 1. Patients treated: prior therapy and doses given

Pt no.	Age	Sex	Diagnosis	Prior surgery	Prior radiation	Chemotherapy	Performance status (ECOG)	Doses given ($\times 10^4$ units/m^2)		
								1	2	3
1	53	F	Adenocarcinoma, lung	Y	Y	5FU, DDP, MTX	0	1.0	1.0	
2	55	M	Teratoma, thymus	Y	N	DDP, ADR, MTX, 5FU, VCR, 5FU	1	1.0	1.5	
3	53	F	Adenocarcinoma, lung	Y	N	MTX, 5FU, DDP, VCR, ADR	0	1.0	1.0	1.0
4	50	F	Adenocarcinoma, lung	Y	N	5FU, DDP, MTX, VCR, ADR	1	1.5	1.5	
5	62	M	Adenocarcinoma, colon	Y	N	5FU, CF, DDP	0	1.5	1.5	
6	67	M	Renal cell carcinoma	Y	Y	CGP 6809, IF	0	1.5	2.25	5.0
7	52	M	Mesothelioma, pleura	Y	N	MTX, 5FU, DDP, VCR, ADR	2	1.5		
8	51	F	Adenocarcinoma, lung	Y	N	DDP, 5FU, MTX, ADR, VCR, 5FU/CF	0	2.25	5.0	10.0
9	48	F	Renal cell carcinoma	Y	N	IF, VBL	2	2.25	5.0	
10	68	M	Adenocarcinoma, rectosigmoid	Y	N	5FU, MeCCNU, VCR, Strep, DAMP, CGP15720A, 5FU/CF				
11	68	M	Adenocarcinoma, rectum	Y	N	5FU/CF	0	5.0	10.0	20.0
12	52	M	Renal cell carcinoma	Y	N	IF	0	5.0	10.0	20.0
13	57	F	Liposarcoma, small bowel, mesentery	Y	Y	CTX, ADR, VCR, DTIC, DDP	2	5.0	10.0	
14	49	M	Adenocarcinoma, rectum	Y	N	MTX, 5FU, 5FU/CF, DDP	0	10.0	20.0	20.0
15	57	F	Adenocarcinoma, rectosigmoid	Y	Y	5FU	0	10.0	20.0	30.0
16	54	M	Renal cell carcinoma	Y	N	VBL, BLEO, CCNU	0	10.0	20.0	20.0
17	70	M	Renal cell carcinoma	N	N	None	1	20.0	30.0	36.0
18	29	F	Renal cell carcinoma	Y	N	None	0	20.0	30.0	30.0
19	45	F	Adenocarcinoma, breast	Y	N	Nolvadex, tamoxifen, high-dose progesterone, Cytadren, 5FU, MTX, VCR, CTX, ADR	2	20.0	30.0	36.0
20	35	F	Renal cell carcinoma	Y	N	None	1	30.0	36.0	36.0
21	35	F	Chordoma, sacral bone	Y	N	VCR, ADR, DTIC, DDP	0	30.0	20.0	
22	56	M	Adenocarcinoma, stomach	Y	N	5FU, ADR, Me-CCNU	0	30.0	36.0	48.0
23	38	M	Transitional cell carcinoma, bladder	Y	N	DDP, MTX, DDP, VBL	0	30.0	36.0	
24	60	M	Adenocarcinoma, scalp (sweat gland)	Y	Y	None	1	36.0	48.0	48.0
25	58	F	Melanoma	Y	Y	BCNU, ACT D, VCR, DTIC, DDP	1	36.0	36.0	

(Table 1 continued)

Abbreviations: Y, yes; N, no; 5-FU, 5-fluorouracil; MeCCNU, 1-(2-chloroethyl)-3(4-methylcyclohexyl)-1-nitrosourea; BLEO, bleomycin; MTX, methotrexate; ADR, doxorubicin; DDP, cisplatin; VCR, vincristine; CTX, cyclophosphamide; VBL, vinblastine; BCNU, 1,3-bis-chloro(2-chloroethyl)-1-nitrosourea; DTIC, dacarbazine; ACT.D, actinomycin D; CF, citrovorum factor; CCNU, 1-(2-chloroethyl)-3(cyclohexyl)-1-nitrosourea; IF, interferon; Strep, streptozotocin; CGP 6809, ethyl 6-deoxy-3,5 di-O-methyl 6-(3 methyl-3-nitrosoureido)-alpha-D-glucofuranoside; CGP 15720A, 1-[2-[2-(4-pyridyl)-2-imidazoline-1-yl]-ethyl]-3-(4-carboxy-phenyl)urea; DAMP, 2,4-diamino-5-adamantyl-6-methyl pyrimidine ethane sulfonate

Table 1 (continued)

Pt no.	Age	Sex	Diagnosis	Prior surgery	Prior radiation	Chemotherapy	Performance status (ECOG)	Doses given ($\times 10^4$ units/m^2)		
								1	2	3
26	63	M	Adenocarcinoma, rectum	Y	N	5FU, DDP, CGP6809, 5FU/CF	1	36.0	48.0	36.0
27	63	M	Renal cell carcinoma	Y	N	None	1	48.0	36.0	36.0
28	27	M	Melanoma	Y	N	Act-D, BCNU, VCR, DTIC, DDP	1	48.0	36.0	
29	26	F	Synovial cell sarcoma	Y	N	ADR, DTIC, DDP, MTX, CF, VCR, ACT-D, CTX, predmustine, ifosfamide	1	36.0	36.0	

Table 2. Fever following treatment with rH-TNF

Dose ($\times 10^4$ units/m^2)	N[a]	No. with temp. $>38°$ (%)	Highest temperature (°C)	
			Mean	Range
1	6	3 (50)	37.9	37.2–38.6
1.5	7	5 (71)	38.1	37.3–38.9
2.25	4	1 (25)	38.3	37.3–39.5
5	6	0 (0)	37.5	37.0–37.6
10	7	2 (29)	37.7	37.0–38.5
20	10	6 (55)	38.1	37.4–39.0
30	10	6 (67)	38.2	37.2–39.5
36	15	9 (56)	38.2	37.0–39.5
48	6	3 (50)	38.0	37.4–38.8

[a] N = number of courses at each dose level

cin 12 h and 1 h before drug infusion and 2 h after the end of drug infusion. Normal saline was infused at the rate of 1 l every 12 h, beginning 12 h before drug infusion and continuing until vital signs were stable.

Pharmacokinetic studies. Blood for the measurement of TNF levels was drawn at 15, 30, 45, and 60 min during the infusion, and at 5, 10, 15, 20, 30, 45, 60, 120, 240, 360, 720, and 1080 min after the end of drug infusion into heparinized tubes; the plasma was immediately separated by centrifugation and assayed for TNF levels by an ELISA assay [6].

Data were analyzed by noncompartmental pharmacokinetic analysis using the program LAGRAN on a Sperry PC computer [9]. The proposed starting dose was 1×10^5 units/m^2, based on the toxicity in the dog, the most sensitive animal species tested (H. Hayashi 1985, personal communication). However, at the request of the Bureau of Biologics the starting dose used was 1×10^4 units/m^2.

Each patient received a maximum of three doses at intervals of 3 weeks. The planned escalation was as follows: in the absence of toxicity, 100% escalation, in the presence of toxicity up to and including grade 1, 50% escalation: in the presence of grade 2 toxicity, no escalation: and in the presence of toxicity greater than grade 2, dose de-escalation. Each patient had the dose escalated if appropriate over the course of the three doses administered, but a minimum of three new patients were added at each dose level.

Table 3. Hypertension

Dose (units/m$^2 \times 10^4$)	1	1.5	2.25	5	10	20	30	36	48
N	6	7	4	6	7	11	9	16	6
Maximum increase in blood pressure in first 24 h after treatment (mmHg, systolic/diastolic)									
Systolic Mean	32	44	31	30	21	27	15	19	11
(Range)	(24–42)	(16–68)	(10–46)	(10–48)	(8–78)	(8–78)	(4–38)	(2–50)	(0–28)
Diastolic Mean	24	16	19	17	14	14	14	12	6
(Range)	(2–54)	(4–24)	(10–24)	(4–26)	(8–24)	(0–24)	(2–30)	(0–36)	(0–16)
Maximum blood pressure in first 24 h after treatment									
Systolic 170–199 mmHg or diastolic 100–109 mmHg	1	6	2	6	2	5	4	3	0
Systolic >200 mmHg or diastolic >110 mmHg	0	1	1	0	3	1	0	2	0
Total	1	7	3	6	5	6	4	5	0
%	17	100	75	100	71	55	44	31	0

Table 4. Hypotension

Dose (units/$m^2 \times 10^4$)	1	1.5	2.25	5	10	20	30	36	48
N	6	7	4	6	7	11	9	16	6
Maximum decrease in blood pressure in first 24 h after treatment (mmHg, systolic/diastolic)									
Systolic Mean	18	21	25	32	25	28	36	33	47
(Range)	(6–30)	(8–42)	(20–34)	(12–44)	(8–44)	(0–54)	(8–58)	(22–52)	(14–70)
Diastolic Mean	15	15	12	26	21	21	29	24	44
(Range)	(0–26)	(6–20)	(2–30)	(10–44)	(10–36)	(6–40)	(4–50)	(14–42)	(10–60)
Minimum blood pressure in first 24 h after treatment									
Systolic 71–90 mmHg or diastolic 41–50 mmHg	1	0	0	1	0	5	4	11	2
Systolic <70 mmHg or diastolic <40 mmHg	0	0	0	0	0	0	2	0	4
Total	1	0	0	1	0	5	6	11	6
%	16	0	0	16	0	45	67	69	100

Table 5. Toxicity of rH-TNF in patients receiving repeated treatment at the same dose[a]

Pt. no.	Dose ($\times 10^4$U/m^2)	Course no.	Max. temp.	Max. BP	Min. BP
1	1	1	38.5	164/80	94/70
	1	2	38.6	160/90	86/60
3	1	1	38.0	136/78	102/58
	1	2	37.2	150/90	84/60
	1	3	37.7	142/90	98/60
4	1.5	1	38.9	172/102	102/70
	1.5	2	38.2	170/100	100/60
5	1.5	1	38.5	210/100	122/72
	1.5	2	37.8	178/106	110/70
14	20	2	39.0	210/110	92/68
	20	3	38.3	142/100	100/70
16	20	2	37.9	120/74	100/70
	20	3	37.8	122/84	90/60
18	30	2	38.0	134/80	90/60
	30	3	39.5	150/88	92/40
20	36	2	39.0	152/90	100/50
	36	3	37.9	140/100	104/50
24	48	2	38.0	160/92	116/50
	48	3	38.4	160/90	80/20
25	36	1	39.3	124/80	80/56
	36	2	39.2	140/68	72/50
26	36	1	37.2	150/88	94/60
	36	3	37.0	140/100	78/50
27	36	2	37.6	150/102	108/68
	36	3	37.2	142/80	110/70
29	36	1	39.1	130/70	90/48
	36	2	38.6	130/72	94/50

[a] Patients who received more than one course at the same dose are listed, with the maximum temperature, maximum and minimum blood pressure on successive doses

However, it soon became apparent that fever and rigors were not dose-related, so the escalation was modified insofar as these side effects were ignored from the point of view of determining escalation.

Courses were considered evaluable for acute toxicity if the patient could be observed for 48 h after drug administration. Courses were considered evaluable for chronic toxicity and for response if the patient could be followed up for a minimum of 3 weeks after administration of the dose of the drug. Criteria for response were those of the ECOG (essentially a decrease by 50% of the product of two diameters, measured at right angles to one another, of a measurable lesion, without an increase in any lesion or the appearance of new lesions).

Results

In all, 29 patients were entered, and they received a total of 72 courses, each course consisting of a single 1-h infusion of the drug. All courses were evaluable for acute toxicity and 71 were evaluable for chronic toxicity, 1 patient having died on day 5 of disease-related causes. The patients treated, their diagnoses and prior therapy and the doses received are listed in Table 1. Skin tests with rH-

Table 6. Effect of prior therapy with rH-TNF on toxicity

Dose ($\times 10^4$ units/m^2)	Mean maximum temperature		Mean maximum blood pressure		Mean minimum blood pressure	
	A	B	A	B	A	B
30	38.2	38.3	136/86	142/90	87/50	69/57
36	38.4	38.1	158/86	138/89	91/59	95/60
48	37.8	37.8	137/84	141/83	79/40	77/27

At each of the three highest doses administered, the mean of the highest temperature, highest blood pressure and lowest blood pressure is compared for patients receiving this dose as their first exposure to rH-TNF (A) and patients escalated from a lower dose (B)

Table 7. Other side effects seen after rH-TNF

Dose ($\times 10^4$ units/m^2)	No. of courses	Number with:						
		Chills	Chest tightness	NV	Headache	Peripheral cyanosis	Low back pain	Diarrhea
1.0	6	3	1	2	2	0		
1.5	7	4	3	1	1	4		
2.25	4	2	0	3	1	2		
5.0	6	2	1	0	1	3		
10.0	7	6	1	2	2	5		
20.0	11	6	1	5	2	5		1
30.0	9	5	2	5	4	4		
36.0	16	11	3	6	4	3	3	2
48.0	6	6	0	4	1	1	3	
Total	71	45	12	24	18	27	6	3
%		64	17	34	26	39	9	4

NV, nausea and vomiting
1 pt had shortness of breath, 36.0 dose

Table 8. Hematologic changes after rH-TNF

	No. of courses	No. of patients	Count/mm^3 Nadir or maximum[a]	
			Median[b]	Range[b]
Leukopenia (WBC <4000/mm^3)	10	6	3550	1900–3800
Eosinophilia (Eos count >700/mm^3)	12	6	1150	710–3410
Monocytosis (Mono count >1000/mm^3)	14	11	1189	1008–1632

[a] Nadir for leucopenia maximum for eosinophilia and monocytosis
[b] Median and range are for those courses listed in column 2

Table 9. Hepatotoxicity after rH-TNF

Dose ($\times 10^4$ units/m^2)	N[a]	SGOT (IU/l)		Total
		100–300	>300	
30	9	2	0	2
36	16	5	1	6
48	6	1	1	2
Total	21	8	2	10

Maximum on day 2 (8), day 3 (1), day 7 (1)
[a] Courses evaluable for hepatotoxicity

Table 10. Kinetics of SGOT evaluation after rH-TNF[a]

Pt. no.	Course	Pretreatment	SGOT IU/l		
			Day 2[b]	Day 3	Day 8
19	3	51	130	108	36
20	3	32	102	59	ND
21	1	22	141	258	31
22	2	17	570	140	29
22	3	15	345	137	31
27	1	23	222	78	34
27	3	46	109	56	46
28	1	33	198	107	40
28	2	36	106	75	31

[a] Serial values for SGOT in patients with SGOT >100 IU/l on day 2 or 3
[b] Days 2+3: 24 and 48 h after drug infusion, respectively

Table 11. Pharmacokinetic parameters in 8 patients after rH-TNF

Pt. no.	Total dose (units $\times 10^4$)	CL_p ($L \cdot h^{-1}$)	$t_{1/2}$ (h)	AUC units $\cdot h^{-1} \cdot l^{-1}$
16	38	28.07	0.33	14250
19	40	32.46	0.20	11706
15	51	7.96	0.40	64092
17	57	12.68	0.44	44957
22	57	19.03	0.37	29947
18	60	24.07	0.42	24928
22	65	9.16	0.65	70954
17	68	7.43	0.72	91506

Model independent pharmacokinetic parameters were generated using the program Lagran [9] on a Sperry PC

TNF and tests for TNF antibodies were negative in all patients.

Acute toxicity

The acute toxicities seen were fever, chills, tachycardia, hypertension, hypotension, peripheral cyanosis, nausea and vomiting, headache, chest tightness, low back pain, diarrhea and shortness of breath.

The data on fever are shown in Table 2. It was very variable, occurred at each dose level, was not dose-related, and was not dose-limiting in any patient. It resolved within a few hours of the end of the infusion. Hypertension is summarized in Table 3. It was also not dose-limiting and tended to decrease with increasing dose. It occurred during the infusion and disappeared rapidly after the end of the infusion. Hypotension (Table 4) occurred after the completion of infusions and was very variable, but tended to increase with increasing dose. Since intrapatient escalation was used in this study, but a minimum of 3 new patients were added at each dose level, data in Tables 2, 3

and 4 are the combined data from new patients and those who had formerly received a lower dose. To evaluate whether toxicity was different for these two groups, the data on temperature and blood pressure effects in 14 patients who received the same dose more than once have been collected in Table 5. From these data it does not appear that there is a consistent trend for the second dose to be less toxic than the first. A further analysis for the three highest doses is presented in Table 6. The mean of the maximum temperature and maximum and minimum blood pressure for the patients for whom these doses were the initial exposure to rH-TNF are compared with the same parameters for patients for whom these doses were given at their second or third exposure to the drug. Again, no trend towards less toxicity in patients previously exposed can be detected.

Other acute toxicities are shown in Table 7 with the percentages of courses in which they occurred. Chills generally occurred during the drug infusion and were occasionally severe, but were never dose-limiting. They usually remitted spontaneously with the end of the infusion, sometimes before. Peripheral cyanosis was seen in a total of 14 patients, and in 4 of these arterial blood gases were evaluated, but no hypoxia was noted. Nausea, vomiting and headache were mild (grade 0–2). Complaints of chest tightness were noted in 17% of courses. It was not accompanied by any EKG changes. Cardiac enzymes were evaluated in patients 2, 9, and 14, but were not indicative of cardiac damage.

Other toxic manifestations

Hematologic changes are summarized in Table 8. Leukopenia was inconsequential and thrombocytopenia was not seen. Eosinophilia was noted in a few patients and tended to recur in subsequent courses if noted initially in the first course. Monocytosis was also noted in some patients. None of these changes was dose-related or of major clinical significance.

An early rise in SGOT without change in serum bilirubin was noted in some patients at the highest doses. These are summarized in Table 9. The SGOT rapidly returned to normal and values were generally within normal limits by the end of the first week following treatment (Table 10).

Mild hypocalcemia, which was asymptomatic and rapidly reversed, was noted in a few patients. Occasional patients showed an increase in fibrin degradation products (≥ 64 μg/ml in 5/72 courses). Fibrin monomer was positive in 5/72 courses. No patient showed both FDP ≥ 64 and positive fibrin monomer. There was no hypofibrinogenemia and no bleeding.

Long term sequelae

There were no delayed toxicities or long-term sequelae in this study (median follow-up 116 days). There were no patient deaths related to the drug administration.

Responses

There were no antitumor responses in this group of patients.

Pharmacokinetic parameters

Below a dose of 20×10 units/m^2, plasma levels were too low for pharmacokinetic measurements. The plasma clearance and plasma decay half-life of 8 patients in whom sufficient plasma values for TNF could be measured are given in Table 11. There is considerable variability in the data which, however, indicate a rapid plasma clearance and short plasma half-life. The postinfusion plasma decay curves for 20, 30 and 36×10^4 units/m^2 are shown in Fig. 1. The data, though preliminary, suggest nonlinear pharmacokinetics of the drug.

Discussion

The recombinant human tumor necrosis factor used in this study is a human protein from *E. coli*, which has shown a marked cytotoxic effect in some tumor types but, in vitro, has no toxic effect against normal human diploid cells. It produces hypotension in dogs, an effect which can be partially ameliorated by indomethacin. Preliminary reports of clinical studies with human TNF have appeared [1, 3, 7, 11, 12], including a preliminary report of the present study [4], but no full report of human phase I study has been published. The drug has been given i. v. in infusions lasting from 30 min to 24 h, and by the i. m., s. c., and i. t. (intratumoral) routes. The study with 24 h continuous infusion [11] was conducted with the material used in the present study (rH-TNF Asahi): in the other clinical trials other preparations were used. Because of this and because the units used differ among the studies, it is difficult to compare the results of these trials on a quantitative basis. Qualitatively the following have been reported in one or more of the published abstracts: chills, fever, nausea, vomiting, headache, back pain, malaise, fatigue, diarrhea, transient hypertension, hypotension, hypercoagulability, transient neutropenia, rise in SGOT, and rise in alkaline phosphatase.

In the present phase I study of TNF a number of toxicities were seen. Most of these were acute toxicities of the type seen with the injection of foreign protein, including fever, chills, hypertension, and hypotension. They were seen either during the infusion itself or during the first 24 h after the drug treatment, and resolved rapidly. Some of them were marked in some patients and hardly noticeable in others, did not increase in severity with repetitive dosing with the drug and were not dose-related. Indeed, the hypertension appeared to show a tendency to be less severe with the higher than with the lower doses. Hypotension, on the other hand, was dose-related. It occurred after the end of the infusion, at variable periods up to about 20 h. It occurred in spite of infusions with saline, and at the highest dose evaluated, 48×10^4 units/m^2, periods of marked hypotension which were briefly symptomatic were noted. Infusions of dextran were occasionally used, but no other blood pressure support measures were taken. Organ-related toxicities, such as myelosuppression and hepatotoxicity, were also seen, but were usually mild and rapidly reversible. The maximum dose reached in the present study was 48×10^4 units/m^2, and further escalation was limited by hypotension.

Of interest in the present trial is the much lower dose reached than that reached by other investigators using the same material. Kimura et al. [8] reached a dose of 160×10^4 units/m^2 in a phase I trial. The dose-limiting toxicity was hepatotoxicity. Hypotension was seen in 27% of patients, and the maximum tolerated dose (MTD) was $90-120 \times 10^4$

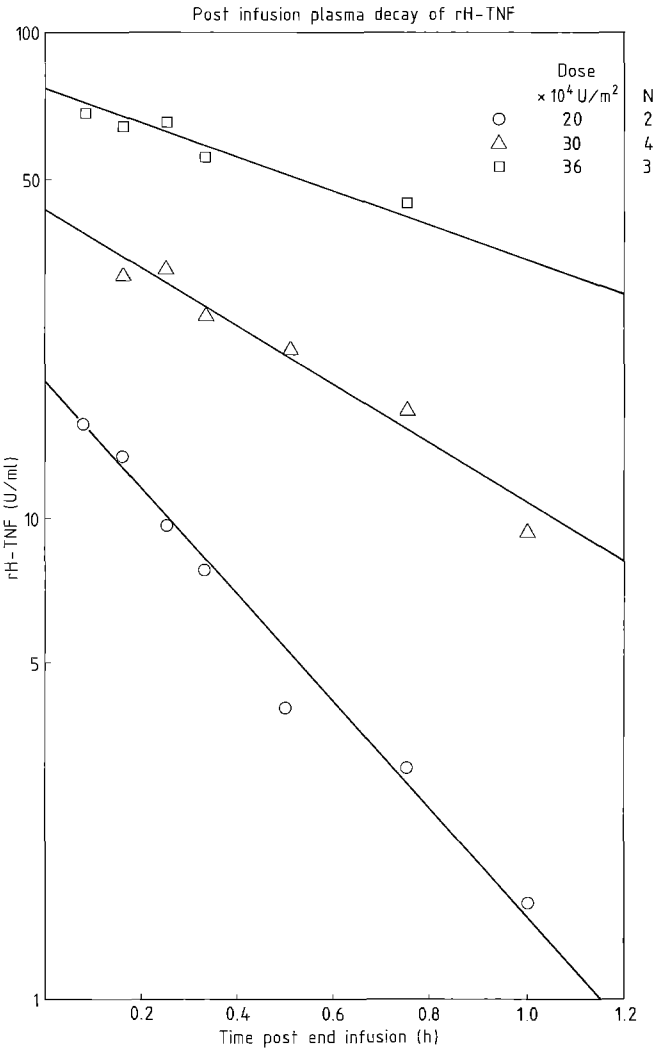

Fig. 1. Plasma was assayed for rH-TNF as described in "Materials and methods". Each *point* represents the mean value for the plasma level at that time for the number of patients studied

units/m^2. The reason for this marked difference in toxicity is not clear. Although most of the patients in the present trial had had multiple prior chemotherapy and had advanced disease (Table 1), in general, they had good performance status and pretreatment blood pressures were in the normal range at the highest dose explored (Table 4). All patients treated with the highest dose were receiving concomitant medication, but no pattern suggestive of drug interaction could be discerned. A major difference may be the level of blood pressure support used in the two studies. Since this was a phase I study designed with the objective of defining the MTD and the nature of the dose-limiting toxicities, it was not felt appropriate to attempt to go beyond the MTD by introducing more vigorous methods to modify the hypotension which was the dose-limiting toxicity. Such methods are appropriate for further studies with the drug, provided they do not, at the same time, modify the potential antitumor activity. More frequent administration of the drug, such as daily dosage, might be expected to allow increased amounts of drug to be given, because it might induce tachyphylaxis of the acute toxicity. We are currently conducting studies with this approach. A number of agents have been described which may modify the hypotensive effect of rH-TNF, and it is planned to explore these, in conjunction with more frequent drug administration, if it can be demonstrated that they do not modify the antitumor activity of the drug.

On the basis of the data in this study the recommended starting dose for phase II studies of the single dose is 48×10^4 units/m^2.

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Note added in proof: Since this paper was written a full report of a phase I study of recombinant tumor necrosis factor in cancer patients has appeared (Blick M, Sherwin SA, Rosenblum M, Gutterman J. Cancer Research 47: 2986–2989, June 1, 1987).

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