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Original Paper

Recombinant Tumour Necrosis Factor in the Local Therapy of Malignant Pleural Effusion

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rHuTNF was locally applied to 26 patients with diverse advanced tumours and malignant pleural effusions following maximum possible drainage of their pleural cavities. 46 instillations (an average of 1.8 per patient) with doses between 0.10 mg and 0.50 mg were carried out. The total doses ranged from 0.15 mg to 1.01 mg per patient. 41% of the instillations resulted in flu-like symptoms, 35% fever/chill, 24% fatigue/malaise, 11% nausea/vomiting and 11% chest pain. All toxicities were fully reversible and could be treated successfully. There was no apparent relation between dose and side-effects. Of those patients treated primarily with TNF, 87% did not suffer from any recurrent effusion within 4 weeks after treatment. In patients who had already been treated employing other methods, this figure was 86%. Complete drainage of the pleural cavity was not absolutely necessary before application of TNF. Intrapleural instillation of TNF appears to be an effective method for achieving pleurodesis with relatively few side-effects and can be successful even after other methods have failed. It is a method which can also be applied to patients who have a poor general state of health.

Key words: tumour necrosis factor, pleural effusion, palliation, malignancies

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INTRODUCTION

IN MOST cases of advanced cancer, the patients' quality of life is probably reduced by dyspnoea as well as pain and ileus. Often, the breathing problems are caused by pleural effusions. Instillation of sclerosis-inducing substances often diminishes exudation, although there are some obvious side-effects. In case of resistance to therapy and recurrent pleural effusions, surgical measures are advisable, such as pleural ectomy, pleuroperitoneal shunts or talc-insufflations. However, seriously ill patients may be unable to cope with such measures, and it is obvious that there is an urgent need for an efficient method of treating malignant effusions without too many side-effects.

In vitro, many human cancer cell lines are sensitive to the cytolytic effects of tumour necrosis factor (TNF) [5]. In phase I studies, recombinant human TNF has been found to be very toxic when administered systematically. The dose-limiting toxicity was hypotension [3, 16]. This is unfortunate as the antitumour properties of TNF appear to require the maximum dose of TNF. Therefore, the clinical use of TNF may be restricted to local applications [2]. After promising results were achieved when TNF was instilled intraperitoneally to treat malignant ascites [13, 15], intrapleural instillation of TNF seemed promising for malignant pleural effusions.

Here, we report on the palliative treatment of 26 patients with malignant effusions, using intrapleural instillation of recombinant human tumour factor (rHuTNF). The effect of this local immunotherapy and its side-effects during the first 4 weeks after instillation and during the remainder of the patients' lifetime were investigated.

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PATIENTS AND METHODS

From August 1990 to October 1994, 26 patients with diverse advanced tumours received pleurodesis with

rHuTNF (Knoll AG, D-67061, Ludwigshafen, Germany) for symptomatic malignant pleural effusion, which were detected on ultrasound/CXR-ray examination. The patients' details are listed in Table 1. 24 patients had previously undergone chemopleurodesis, but subsequently relapsed. Before application of TNF, the following sclerosing substances had been intrapleurally instilled: bleomycin (60 mg), tetracycline-HCl (10 mg/kg body weight), mitoxantrone (16–30 mg), fibrin glue (10 ml) or 5-fluorouracil (1000 mg). 2 patients received pleurodesis with rHuTNF primarily.

The indication to perform pleurodesis were symptoms related to effusion such as dyspnoea, the sensation of intrathoracic pressure, pain, cough, fear, and the feeling of being clammy. A CXR was carried out before pleural drainage and before application of TNF. We attempted to form three different categories: 0 = no effusion, + = effusion in the phrenicocostal sinus, + + = effusion in the phrenicocostal sinus and in other locations. The volumes of effusion tapped are shown in Table 1.

If symptoms recurred within one week after TNF instillation, TNF was re-instilled. In these cases, the application of TNF was continued in patients with malignant ascites [13, 15]. Only patient 26 could not be treated in this way because of his rapid decline. If a pleural tap was needed within 4 weeks after instillation, this was looked upon as recurrence [7, 10].

Table 1. Patients' characteristics and therapy

Patient no.	Sex	Age (years)	KI	Tumour	Pleurodesis agent before TNF	Pleural site	Aspiration volume (ml)	TNF dose (mg)
1	m	68	30	Lung		l	1900	0.15
							900	0.15
							300	0.15
2	m	65	30	Kidney		r	2750	0.15
							1200	0.15
3	f	62	30	Ovary	2 X Mitoxantrone	r	3300	0.15
							2800	0.25
							900	0.25
4	f	67	80	Breast	Bleomycin	r	1600	0.15
5	f	51	80	Breast	Mitoxantrone and fibrin glue	l	3050	0.15
6	m	54	60	Colon Prostate	3 X 5-Fluorouracil	l	1650	0.15
7	f	74	80	Breast	Bleomycin	l	700	0.15
8	f	43	60	Breast	Bleomycin	r	800	0.15
9	f	52	80	Breast	Bleomycin	l	1200	0.15
10	f	70	50	Lung	Mitoxantrone	r	2900	0.15
							1600	0.15
							700	0.15
11	f	62	30	Breast	Mitoxantrone	l	3150	0.15
							1900	0.15
12	f	60	60	Breast	2 X Bleomycin	l	400	0.20
							250	0.10
							500	0.20
13	m	78	60	NHL	6 X Tetracycline and 1 X bleomycin	l	1800	0.25
							1000	0.25
14	f	36	70	Kidney	2 X Mitoxantrone	l	1500	0.38
							900	0.38
							1000	0.25
15	f	88	50	Breast	Bleomycin	l	2400	0.25
16	f	65	50	Breast	Bleomycin	r	1300	0.25
17	f	72	60	Pancreas	Bleomycin	r	750	0.25
18	f	59	70	Breast	2 X Mitoxantrone	r	600	0.25
							320	0.25
							250	0.25
19	f	59	70	Breast	Bleomycin	r	2100	0.25
20	m	54	60	Lung	2 X Bleomycin	r	600	0.25
							650	0.25
21	f	63	80	Ovary	Bleomycin	l	1500	0.25
22	f	40	70	Breast	2 X Bleomycin	l	1000	0.25
							600	0.25
23	f	47	60	Breast	Bleomycin	l	1700	0.25
24	f	68	70	Breast	Bleomycin	r	850	0.25
					and mitoxantrone		500	0.25
25	f	48	30	Breast	2 X Mitoxantrone	l	3600	0.25
								0.25
26	f	61	90	Breast	Bleomycin	r	3500	0.50

l, left; r, right; NHL, non-Hodgkin's lymphoma; KI, Karnofsky index.

The doses applied are shown in Table 1. 6 patients (patients 4–9) received only a single dose of 0.15 mg of TNF, 2 patients received two doses (patients 2 and 11) and 2 patients received three doses (patients 1 and 10). 6 patients (patients 15–17, 21, 23) received a single dose of 0.25 mg, 4 patients received the two doses (patients 13, 20, 22 and 25) and 2 patients received three doses (patients 18 and 24). One patient was given 0.50 mg TNF intrapleurally (patient 26) and 3 patients (patients 3, 12, 14) received other combinations (Table 1). An average of 1.8 instillations per patient was administered with a total of 46, intrapleural instillations. The average single dose was 0.22 mg. The total dose of TNF administered ranged from 0.15 mg to 1.01 mg. The average total dose was 0.39 mg.

TNF pleurodesis was carried out using a needle or a very thin catheter. Maximum drainage of the pleural cavity was carried out. The pulmonary unfolding was monitored by means of ultrasound or CXR and, if necessary, the position of the drain was corrected. Paracetamol (1000 mg) or 100 mg of indometacine were administered 30 min before TNF instillation in order to prevent side-effects. The available rHuTNF lyophilisate was diluted in 50 ml of a 0.9% NaCl solution, which was stabilised by 0.5% human albumin and instilled. Once the drain had been removed, the TNF solution was distributed in the pleural cavity by frequent change of position over a period of 6 h. TNF was re-instilled if symptoms recurred within 1 week or there was more than 1000 ml of intrapleural fluid.

All patients treated with TNF were monitored until they died of their tumour. If no symptoms caused by the effusion occurred, CXR were carried out 4, 8, 12, 24, 36, 48 and 60 weeks after TNF pleurodesis. Patients without tumour-related symptoms were reviewed every 3 months. In case of symptomatic disease, the patients concerned were reviewed earlier as appropriate.

When TNF became unavailable for medical use in October 1994, the trial was terminated.

RESULTS

Patient details

The 26 patients who underwent treatment included 21 women and 5 men with advanced tumours and cytologically proven malignant pleural effusions (Table 1). The average (mean) age of the patients was 61.5 years (range 36–88 years); their average (mean) Karnofsky index was 60% (range 30–90). The malignancies are listed in Table 1. One man (patient 6) suffered from carcinoma of the colon and carcinoma of the prostate gland as a secondary tumour. Presumably the pleural exudate was due to metastatic disease caused by the carcinoma of the colon in this case. 4 patients received additional hormonal medication, 7 patients cytostatic medication and 15 were not given any systemic cytotoxic medication simultaneously. The left pleural cavity was affected 14 times and the right pleural cavity 12 times. Total drainage of the pleural cavity before the last instillation of TNF (using CXR to monitor this) was achieved in 16 patients (patients 7, 8, 9, 12–20, 22, 23, 24 and 26). Patients 4, 6, 21 and 25 retained effusion in their phrenicocostal sinus, with patients 1, 2, 3, 5, 10 and 11 retaining even more fluid. Prior to the first application of TNF, the average (median) aspirated amount of exudate was 1625 (range 400–3600 ml).

Side-effects

In spite of prophylactic application of 1000 mg of paracetamol or 100 mg of indometacine, many patients complained of flu-like symptoms after 19 instillations (41%), followed by fever/chill after 16 instillations (35%), fatigue/malaise after 11 (24%), nausea/vomiting after 5 instillations (11%) and chest pain after 5 instillations (11%) (Table 2). 12/17 (71%) instillations resulted in flu-like symptoms after a single dose of 0.15 mg. Only one patient (patient 13; non-Hodgkin's lymphoma) developed fever and chill equivalent to WHO grade III after the first instillation. In all other cases, the side-effects did not exceed WHO grade II. All toxicities were fully reversible and responded well to adequate symptomatic therapy.

Therapeutic results

Recurrence following completion of the TNF treatment with the corresponding aspiration volume and survival times are listed in Table 3.

Survival ranged from 3 to 72 weeks following pleurodesis. Mean survival was 16.4 weeks. 3 patients died within 4 weeks (patients 1, 14 and 20) after therapy as a result of their advanced tumours. There was no indication that these patients had died of side-effects of pleurodesis carried out previously.

Three of the 23 remaining patients had to be repunctured within 4 weeks due to recurring symptoms of pleural effusion. Thus, the complete response rate was 20/23 (87%) over 4 weeks (according to Hausheer and Yarbro [7] and Ostrowski [10]; Table 4).

Eighty-six per cent of those patients who had been primarily treated with conventional chemopleurodesis and had survived local TNF treatment for at least 4 weeks had no recurrence (Table 4).

If all recurrences of effusions are considered, 5 patients (patients 8, 14, 18, 23 and 26) required aspirations, while 21 patients (81%) did not relapse (Table 3). The shortest period before another aspiration had to be performed was 0 weeks, the longest 40 weeks.

Table 2. Dose escalation and side-effects

	rHuTNF dose (mg)						
	0.10	0.15	0.20	0.25	0.38	0.50	Total
Fever/chills	0	5 (29%)	0	8 (35%)	2	1	16 (35%)
Nausea/vomiting	1	0	1	1 (4%)	2	0	5 (11%)
Chest pain	0	2 (12%)	0	2 (9%)	0	1	5 (11%)
Fatigue/malaise	0	5 (29%)	0	6 (26%)	0	0	11 (24%)
Flu-like	0	12 (71%)	0	6 (26%)	0	1	19 (41%)
No. of treatments	1	17	2	23	2	1	46

Table 3. Results of TNF pleurodesis

Patient no.	Residual volume	Aspirated volume 1 week	2 weeks	3 weeks	4 weeks	Time to relapse (weeks)	Time to death (weeks)
1	++	0	0	0		*	3
2	++	0	0	0	0		6
3	++	0	0	0	0		14
4	+	0	0	0	0		72
5	++	0	0	0	0		23
6	+	0	0	0	0		37
7	0	0	0	0	0		8
8	0	0	600			1	32
9	0	0	0	0	0		19
10	++	0	0	0	0		7
11	++	0	0	0	0		8
12	0	0	0	0	0		7
13	0	0	0	0	0		8
14	0	0	0	0	1000	3	13
15	0	0	0	0		*	3
16	0	0	0	0	0		4
17	0	0	0	0	0		4
18	0	0	0	0	0	40	64
19	0	0	0	0	0		25
20	0	0	0	0		*	3
21	+	0	0	0	0		28
22	0	0	0	0	0		10
23	0	0	0	0	0	5	5
24	0	0	0	0	0		13
25	+	0	0	0	0		6
26	0	500				0	5

0 = no effusion, + = effusion in the phrenicocostal sinus, + + = effusion in the phrenicocostal sinus and in other locations before last TNF instillation.
*Death without relapse within 4 weeks.

Patients who still had remnants of effusion after pleural drainage subsequently relapsed. However, the pleural cavity could be drained almost completely in all those patients who had to have a second paracentesis because of a recurrent effusion.

DISCUSSION

Tumour necrosis factor is very effective in the local treatment of malignant ascites with only moderate toxicity [18]. Sistermanns and associates [15] in particular reported the highly promising palliative therapy of ascites in advanced tumours. Räth and associates [13] were able to demonstrate complete or partial remission in 22 out of 29 patients with ascites by installing TNF intraperitoneally. Therefore, it seems advisable to treat patients with malignant pleural effusions with rHuTNF palliatively.

Of 23 patients who were still alive 4 weeks after pleurodesis, 87% still had not developed any recurrent effusion. A large proportion of these patients (22) had already undergone unsuccessful conventional pleurodesis (some of them several times). In spite of this definitely negative selection criterion, 86% of the patients did not develop any recurrence after TNF instillation.

These results reveal no apparent link between dose and success which might be due to the low number of cases and the heterogeneity tumours. A local or systemic influence on tumour growth was not discovered in any of the cases. Cytological tests were not possible in those cases treated successfully due to a lack of exudate.

Table 4. Dose escalation and therapeutic effect

	rHuTNF dose (mg) <0.20	>0.20 <0.40	>0.40 <0.60	>0.60 <0.80	>0.8	Total
All ⩾ 4 week survivors						
No relapse ⩾ 4 weeks	5	7	5	3	0	20 (87%)
Relapse < 4 weeks	1	0	1	0	1	3 (13%)
No. of patients	6	7	6	3	1	23
Only pretreated patients surviving ⩾ 4 weeks						
No relapse ⩾ 4 weeks	5	6	5	3	0	19 (86%)
Relapse < 4 weeks	1	0	1	0	1	3 (14%)
No. of patients	6	6	6	3	1	22

In spite of additional hormone therapy or chemotherapy, complete or partial remission of extrapleural tumour was not observed. Only 3 patients responded to hormone therapy (aromatase inhibitor, patients 5 and 18), and 1 patient to tamoxifen (patient 8). These results suggest that the effect on pleural exudation is not a systemic one effected by simultaneous systemic treatment with other agents but a local one caused by TNF.

The side-effects of TNF application were typical of cytokines. Flu-like symptoms were most common. They occurred in 41% of the cases. However, the severity of these symptoms reached grade III (WHO) in only one case, with fever/chill symptoms. In all cases, the side-effects could be eliminated by means of symptomatic treatment and were fully reversible. In view of the palliation achieved, the TNF-induced side-effects were thoroughly acceptable and even seriously ill patients could tolerate them. The lethal outcome in those three cases of patients who died within 4 weeks after TNF instillation were not a result of the cytokine infusion, but of their advanced tumours.

Due to the known toxicity of TNF, which confines doses given systemically to a certain range [3, 16], we applied relatively low doses initially. Since there were only moderate side-effects after local application which could be treated easily, we applied higher doses in the course of this study to enhance the effect and also to avoid unnecessary pleural tapping.

There was no relationship established between dose and severity of side-effects, although most patients received doses of 0.15–0.25 mg. Therefore, there are not enough cases of patients who received different doses in this study to draw relevant conclusions.

In order to achieve pleurodesis in cases of patients with malignant effusion, bleomycin, tetracycline or mitoxantrone were frequently instilled. Ruckdeschel [14] regards bleomycin as the most suitable therapeutic agent to induce pleurodesis. According to the study carried out by Hartmann and associates bleomycin prevented recurrence for at least 30 days in 64% of their patients [6]. The disadvantages of bleomycin are its local and systemic side-effects [9]. Successful treatment in 33% [6] to 86% [17] of all cases was performed using tetracycline. In a comparative study the effect of bleomycin and mitoxantrone both proved to have virtually the same effect [9]. However, the fact that mitoxantrone is absorbed to a greater extent leading to pronounced myelotoxicity is unfavourable. This might interfere with additional cytotoxic therapy and also be a considerable disadvantage in very ill and immunologically compromised patients.

The effectiveness of TNF demonstrated in this study might be higher than that of the well-established conventional methods, although a precise comparison is not possible because of the diverse assessment criteria of the results.

Following unsuccessful attempts at pleurodesis, thoracoscopic talcum insufflation is recommended in patients with tumours or pleuroperitoneal shunts [12]. Both measures certainly do lead to a longer-lasting success rate in a high number of cases [6, 12, 17], but generally require anaesthesia. The very poor state of health of patients with advanced tumours often interferes with surgical management. Thus, for example, the average life expectancy of 26 patients with an average Karnofsky index of 60% is 16.4 weeks (average value), much lower than that of the group examined by Aelony and associates [1]. In this group, the average life expectancy was approximately 50 weeks, which indicates that his patients enjoyed a considerably better state of health.

The success of chemopleurodesis depends on the complete drainage of the pleural gap. Groth and his team were able to record good results just by sufficiently draining the pleural cavity [4]. In contrast, the success of pleurodesis after TNF instillation does not necessarily depend on full unfolding of the lungs (within certain limits).

The precise reason why TNF pleurodesis is effective is not quite clear, neither is the exact mechanism of the beneficial action of TNF on malignant ascites known. Some *in vitro* results indicate a direct tumoricidal effect of TNF [2, 5], but it is also possible that the serous membranes are sealed by TNF [13]. The investigations carried out by Owens and Grimes [11] as well as Liu and associates [8] appear to be informative. Owens and Grimes discovered a significantly increased proliferation of the pleural mesothelium cells as well as the production of collagen under the influence of TNF in rats. From their observations, they concluded that TNF has an important effect on healing processes after pleural injuries [11]. Liu and his team observed an increase of IL-6, IL-8 and TNF in patients after intrapleural application of tetracycline [8]. They thought that this could be explained by the sclerosing effect of tetracycline.

In conventional pleurodesis, the mechanisms are inflammation and sclerosis, whereas cytokines, including TNF, appear to act as important mediators. This could explain the success of direct application of rHuTNF into the pleural cavity. Therefore, it seems worthwhile to continue to investigate systematically the effect of TNF on pleural effusions.

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