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BRIEF REPORT

Efficacy and safety of recombinant human tumor necrosis factor application for the treatment of malignant pleural effusion caused by lung cancer

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Abstract

Malignant pleural effusion (MPE) signifies a poor prognosis for patients with lung cancer. For treating physicians, the primary goals are to achieve sufficient control of MPE and minimize invasive intervention. Recombinant human mutant tumor necrosis factor-alpha (rhu-TNF) has been used in the treatment of MPE. The aim of our research was to evaluate the efficacy and safety of rhu-TNF application via ultrasound-guided chest tube for the treatment of MPE. rhu-TNF was administered as a single dose to 102 patients with MPE caused by lung cancer, and dexamethasone (Dxm, 5 mg) was administered 30 minutes before rhu-TNF in 35 randomly selected patients in order test its ability to prevent side effects. The primary endpoint was the efficacy of the rhu-TNF treatment (disease response rate) and side effects (pain, fever, and flu-like symptoms), evaluated four weeks after instillation. The disease response rate of rhu-TNF treatment was 81.37%. Side effects included 13 (12.75%) patients complaining of flu-like symptoms, 15 (14.71%) with fever/chill, and 14 (13.73%) with chest pain. A significantly higher efficacy was observed for treatment with 3 MU versus 2 MU of rhu-TNF ($P = 0.036$), while the adverse effects were similar. There was no significant association between the dose of rhu-TNF and progression-free survival ($P = 0.752$). In conclusion, our study shows that intra-pleural instillation of rhu-TNF achieves sufficient control of MPE and minimizes invasive intervention.

Introduction

Malignant pleural effusion (MPE) signifies a poor prognosis for patients with lung cancer and impairs quality of life. Although there are systemic therapies available for the treatment of lung cancer, not all patients with MPE can tolerate these. Therefore, local therapy for MPE is needed to alleviate dyspnea and to improve patient quality of life.[1] Tumor necrosis factor-alpha (TNF-α) has been shown to prolong the survival of fibrosarcoma-bearing mice and to inhibit the accumulation of malignant pleural fluid in the thoracic cavity in vivo.[2] Systemic application of recombinant human mutant TNF-α (rhu-TNF) in patients with advanced cancer demonstrated antitumor effects, but the treatment caused side effects, such as vomiting, pronounced hypotension, and mild renal toxicity.[3] Clinical research of TNF has mainly focused on local administration therapies.[4] Application of rhu-TNF for the treatment of MPE by way of intra-pleural instillation has been suggested as an effective method for achieving pleurodesis in a small number of patients.[5]

The principal aim of our study was to evaluate the efficacy and safety of rhu-TNF in a cohort of patients suffering from MPE caused by advanced lung cancer.

Methods

Patients

This retrospective clinical study was performed in a cohort of 102 patients with MPE resulting from lung cancer. Patients received rhu-TNF intra-pleural instillation at our hospital from March 2013 to September 2014. Trial eligibility required: (i) that tumor cells had been confirmed in pleural fluid; (ii) chest radiography and computed tomography (CT) were performed before and four weeks after treatment; (iii) the Karnofsky performance status was required to be > 40;

and (iv) all patients had adequate hematological function and normal renal and hepatic function.

Procedures

All patients received a single dose of rhu-TNF dissolved in saline after maximum drainage of the pleural cavity via ultrasound-guided chest tube. Dexamethasone (Dxm 5 mg) was administered 30 minutes before rhu-TNF intra-pleural instillation in 35 patients, in order to prevent side effects. When the pleural effusion volume decreased to 100 mL or less per day and ultrasound examination of the chest showed complete dissipation of the effusion, the chest tube was removed. Any side effects or complaints were documented. A follow-up chest radiography was taken four weeks after treatment.

Evaluation of primary endpoints

Response criteria according to World Health Organization (WHO) evaluation standards were used: complete response (CR), pleural effusion disappeared completely and the effect lasted for more than four weeks; partial response (PR), plural effusion was reduced by 50% or more, and the condition remained steady for four weeks or more; and no response (NR) when effusion was greater than that defined by PR. CR and PR rates were added to calculate disease response rate (RR). Adverse events were assessed using version 3.0 of the National Cancer Institute Common Terminology Criteria.

Statistical analysis

Descriptive statistics was used to characterize patient disease RR and adverse events. Rates were compared by χ^2 test. Fisher's exact test was used to examine statistical differences. Kaplan-Meier method was applied in univariate analysis to estimate survival probabilities. $P < 0.05$ was considered statistically significant. Statistical analysis was conducted using SSPS version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Therapeutic results

The patient demographic, clinical characteristics, and rhu-TNF dose are listed in Table 1. A comparison of the RR of the 35 patients treated with Dxm before rhu-TNF application are shown in Table 2. The therapeutic results for the primary endpoint, RR, of each dose are presented in Table 3. The disease RR of the entire cohort was 81.37% ([36 + 47]/102). The disease RR in the Dxm group was 80% ([12 + 16]/35), while in the rhu-TNF group without Dxm, the disease RR was 82.09% ([24 + 31]/67). Efficacy between the rhu-TNF groups with and without Dxm was not significantly different (Table 3; $P = 0.794$). A significantly higher efficacy was observed for treatment with 3 MU versus 2 MU (Table 3; $P = 0.036$); however, there was no significant difference in progression-free survival (PFS) (Fig. 1, $P = 0.752$) or efficacy between the 2 MU and 3 MU Dxm/rhu-TNF groups (Table 2; $P = 0.34$). There was no evidence to indicate that the subtype of lung cancer affected the outcome of rhu-TNF application in the treatment of MPE (Table 3).

Table 1 Demographic and clinical patient characteristics

Group	Number of patients
Age (years)	61
Gender, *n* (%)	
Male	45 (44.12)
Female	57 (55.88)
Lung cancer, *n* (%)	
Left	54 (52.94)
Right	48 (47.06)
Subtype of lung cancer, *n* (%)	
Ad	85 (83.33)
Sq	10 (9.80)
SCLC	7 (6.87)
rhu-TNF dose (MU), *n* (%)	
1.0	3 (2.94)
2.0	53 (51.96)
2.5	2 (1.96)
3.0	41 (40.20)
4.0	1 (0.98)
5.0	2 (1.96)

n = 102. Ad, adenocarcinoma; MU, million IU; SCLC, small cell lung cancer; Sq, squamous carcinoma; rhu-TNF, recombinant human mutant-tumor necrosis factor.

Adverse events of recombinant human mutant-tumor necrosis factor treatment

The side effects observed for each dose for all rhu-TNF-treated patients are listed in Table 4, and the side effects for the 35 patients receiving Dxm before rhu-TNF application

Table 2 Therapeutic result and side effects for Dxm before rhu-TNF treatment

Group	Number of patients	CR	PR	NR	Fever	Pain	Flu-like	*P*-values RR
1.0 MU	1	1	0	0	0	0	0	
2.0 MU	9	1	4	4	0	1	0	
3.0 MU	**24**	**10**	**12**	**2**	**3**	**0**	**0**	***0.34**
5.0 MU	1	0	0	1	0	4	0	

**P*-values <0.05 were considered statistically significant. *n* = 35. CR, complete response; Dxm, dexamethasone; MU, million IU; NR, no response; PR, partial response; RR, response rate; rhu-TNF, recombinant human mutant-tumor necrosis factor.

Table 3 Therapeutic result of rhu-TNF intra-pleural instillation

Group	CR	PR	NR	*P*-values RR
1.0 MU	1	2	0	
2.0 MU	**16**	**23**	**14**	
2.5 MU	0	2	0	
3.0 MU*	**18**	**19**	**4**	***0.036**
4.0 MU	1	0	0	
5.0 MU	0	1	1	
Total, *n* (%)	36 (35.29)	47 (46.08)	19 (18.63)	
Dxm before rhu-TNF				0.794
Yes	12	16	7	
No	24	31	12	
Ad	30	40	15	
Sq	4	4	2	
SCLC	2	3	2	

**P*-values <0.05 were considered statistically significant; $P = 0.036$ between the 2.0 MU and 3.0 MU groups. $n = 102$. Ad, adenocarcinoma; CR, complete response; Dxm, dexamethasone; MU, million IU; NR, no response; PR, partial response; SCLC, small cell lung cancer; Sq, squamous carcinoma; rhu-TNF, recombinant human mutant-tumor necrosis factor.

are shown in Table 2. In all cases, the side effects did not exceed WHO grade II severity. When the incidence of fever and pain between the Dxm before rhu-TNF and without Dxm groups was analyzed, *P*-values were >0.05 (Table 4), although the rate of fever and pain symptoms appeared to be decreased in the Dxm group and no flu-like symptoms were observed. There were no significant differences in side effects, such as fever, chest pain, and flu-like symptoms, between the 2 MU and 3 MU rhu-TNF groups, with *P*-values of 0.24, 0.57, and 0.10, respectively (Table 4).

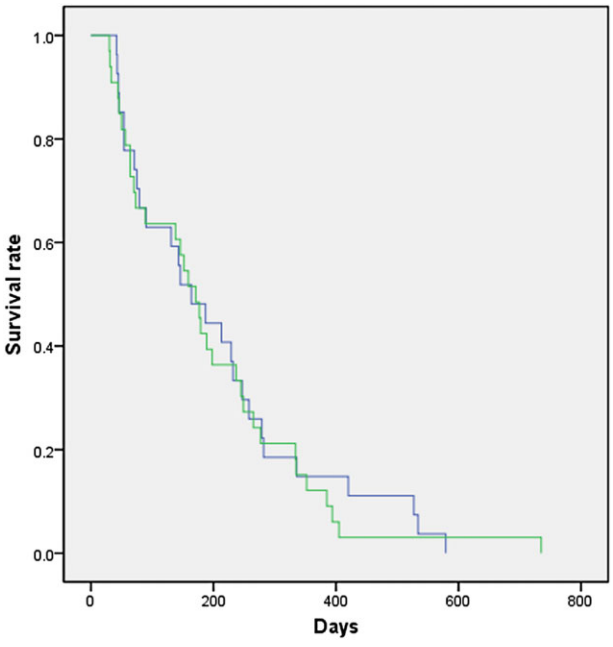

Figure 1 Kaplan-Meier curves of progression-free survival. (—) 2 MU, (—) 3 MU.

Table 4 Side effects of rhu-TNF intra-pleural instillation

Group	Fever	Pain	Flu-like
1.0 MU	0	0	0
2.0 MU	9	7	8
2.5 MU	0	0	1
3.0 MU	5	6	3
4.0 MU	0	0	1
5.0 MU	1	1	0
total, *n* (%)	15 (14.71)	14 (13.73)	13 (12.75)
Dxm before rhu-TNF			
Yes	3	5	0
No	12	9	13
P-values (2.0 and 3.0 MU)	*0.24	*0.57	*0.10

**P*-values <0.05 were considered statistically significant. $n = 102$. Dxm, dexamethasone; MU, million IU; rhu-TNF, recombinant human mutant-tumor necrosis factor.

Discussion

At present, few treatments to efficiently control MPE caused by lung cancer are available. Our study, undertaken to evaluate the efficacy and safety of rhu-TNF for the treatment of MPE, showed an RR of 81.37%, which was inferior only to talc.[6] However, the side effects of talc, such as acute pneumonitis and acute respiratory distress syndrome with respiratory failure, were not observed in the rhu-TNF group.[7,8] rhu-TNF therapy has a similar RR as treatment with bleomycin, displaying a 30 day response rate of 84.3%.[9]

The most commonly used dose of rhu-TNF in this study was 2 MU or 3 MU intra-pleural instillation via chest tube. The results show that 3 MU has better efficacy than 2 MU, while adverse events and PFS are comparable. Therefore, we recommend the application of 3 MU rhu-TNF as a single dose for the treatment of MPE. Because of the relatively small sample sizes of the 4 MU and 5 MU groups, further research is needed to evaluate any additional beneficial effects of higher doses.

In patients receiving Dxm before rhu-TNF intra-pleural instillation, the incidence of adverse events was reduced compared to the patients who received no Dxm treatment. However, no significant difference in efficacy was found. Therefore, a combined Dxm/rhu-TNF treatment is recommended to reduce adverse events following treatment.

Although TNF-α has been demonstrated to trigger apoptosis in cancer cells, the mechanism of rhu-TNF for controlling pleural effusion remains unclear.[10,11] It could be speculated that, as a biological modifier of apoptotic pathways, rhu-TNF decreases MPE by killing tumor cells through

induction of apoptosis, regulating the body's immune function.[12,13] More research is needed in order to evaluate the molecular mechanism of the therapeutic effects of TNF for MPE.

The present study was limited in that it was a retrospective trial. Additional randomized and controlled studies are necessary to confirm the beneficial effects of rhu-TNF treatment for MPE. Our study focused on two concentrations of rhu-TNF commonly used in clinical practice; however, a variety of proposed dose groups are necessary to define the optimal rhu-TNF dose for a clinical setting.

In conclusion, the study shows that intra-pleural instillation of rhu-TNF achieved sufficient control of MPE and minimized invasive intervention in a cohort of lung cancer patients.

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Disclosure

No authors report any conflict of interest.

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