·**Clinical Research**·

Clinical research on recombinant human Ad-p53 injection combined with cisplatin in treatment of malignant pleural effusion induced by lung cancer

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【**Abstract**】 **Background and Objective:** p53 gene is one of cancer suppressor genes and its mutation and deletion induces almost all human cancers. This study was to evaluate the clinical efficacy and toxicity of recombinant human Ad-p53 injection (rAd-p53) combined with cisplatin in treatment of malignant pleural effusion induced by lung cancer. **Methods:** A total of 35 cases of malignant pleural effusion were randomly divided into the combined group (n=17) and the single-agent group (n=18). On the basis of systemic treatment (vinorelbine 25 mg/m², Days 1–8, every 3 weeks), the combined group were given intracavitary administration of rAd-p53 (1×10^{12} VP) and cisplatin (40 mg/m²) once a week for 4 weeks. The single-agent group were given the same intracavitary administration as the combined group but without rAd-p53 therapy. **Results:** The total effective rates in the combined group and the single-agent group were 82.35% and 50.00% (P<0.05), respectively. The total modification rates in the combined group and the single-agent group were 64.70% and 33.33% (P<0.05), respectively. The toxicities in the two groups were fever, stethalgia, nausea/vomiting and leukopenia. The toxic reaction in combined group was mainly self-limited fever (P< 0.05), which disappeared automatically after 36 h. **Conclusions:** rAd-p53 and cisplatin is safe and effective for malignant pleural effusion induced by lung cancer. It is worthy of application in clinical treatment.

Key words: recombinant human Ad-p53 injection, malignant pleural effusion, gene therapy, cisplatin

Malignant pleural effusion is one of the common complications of advanced malignant tumors. It is usually accompanied with symptoms of chest distress, dyspnea, racing heart, and chest pain, severely influences the life quality of patients. Therefore, effective control of pleural effusion during the treatment for advanced tumors can improve life quality and prolong survival time. In this study, we used recombinant human Ad-p53 injection (Gendicine, rAd-p53) via central venous catheterization with closed drainage, in combination with cisplatin (DDP) to treat 35 cases of pleural effusion due to lung cancer, and analyzed the treatment efficacy and adverse events.

Materials and Methods

General data

Thirty-five lung cancer patients with malignant pleural effusion were treated in the Oncology Department of the First Affiliated Hospital of Liaoning Medical College between July 2005 and December 2008. These patients were divided randomly into the combination group and the single-agent group. Of the 17 patients in the combination group, 9 were men and 8 were women, aged 40–71 years with a median of 55; 6 had squamous cell carcinoma, 9 had adenocarcinoma, and 2 had large cell carcinoma. Of the 18 patients in the single-agent group, 10 were men and 8 were women, aged 37–75 years with a median of 55; 8 had squamous cell carcinoma and 10 had adenocarcinoma. The diagnoses of malignant pleural effusion were confirmed by thoracic CT examination, color thoracic ultrasound, and cytohistological examination. All patients had a KPS of 60 points for general status, with expected survival of more than 3 months. The results of electrocardiogram (ECG), liver function

examination, kidney function, and routine blood examination were all normal. No patients had received previous chemotherapy, radiotherapy, and biological therapy.

Treatment

Closed thoracic drainage Pleural effusion was localized by color ultrasound. After routine disinfection, draping, and local anesthetization, the trocar was inserted slowly and vertically into the thoracic cavity through the thoracic wall. Pleural effusion was confirmed by withdrawal drainage through the injector. The trocar was withdrawn and central venous catheter was slowly inserted along the guidewire, where the catheter remained at 12 cm in the thoracic cavity. The guidewire was removed after the catheterization. At the external terminal of the catheter, a sterile drainage bag was connected. Initial drainage volume was about 900 mL (with a pause of 20 min for each drainage of 300 mL). Generally, pleural effusion was drained completely within 48–72 h.

Medicines The rAd-p53 injection (1×10^{12} VP per shot) was manufactured by Sibiono Genetic Technology Co., Ltd. in Shenzhen, stored in -20℃, and melted under room temperature for use. DDP injection (30 mg per shot) was manufactured by Hansoh Pharmaceutical Company in Jiangsu.

Drug administration Systemic administration of vinorelbine (25 mg/m^2) was given through intravenous fusion at the first and the eighth days, and repeated every three weeks. Pleural effusion must be completely drained for all patients and the completion was confirmed by color ultrasound. In the combination group, melted rAd-p53 (1×10^{12} VP) was dissolved in 100 mL normal saline (NS) and injected into the thoracic cavity, DDP (40 mg/m^2) was then dissolved in 100 mL NS and administered into the thoracic cavity, dexamethasone (DEX, 10 mg) was also injected to reduce adverse events. The single-agent group was treated with DDP and DEX as described above. In 30 min before drug administration, both groups received bolus injection of ramosetron (0.3 mg) for adequate hydration. In 2 h after drug administration, the patients were ordered to change body position every 15 min to allow wide contact of the thoracic membrane with the drugs. For patients from both groups, drug administration was repeated weekly with four administrations as a cycle; drug administration would be terminated if pleural effusion was eliminated before the completion of treatment.

Primary observation indices

Pulmonary Thoracic CT scan and color ultrasound were performed on all patients before treatment to record changes in pleural effusion and to observe symptoms, body signs, adverse reactions, and life quality. The patients were re-examined in the first week after each drug administration to assess therapeutic efficacy. At the third and the sixth days after drug administration, electrocardiogram (ECG), routine blood test, routine urine test, hepatic function examination, and kidney function examination were performed routinely.

Assessment standard for therapeutic efficacy

The WHO standard was used for assessment of short-term therapeutic efficacy: complete remission (CR) referred to complete removal of pleural effusion for more than four weeks;

partial remission (PR) referred to reduction of pleural effusion by more than 50% and symptom alleviation lasted for four weeks; stable disease (SD) referred to reduction of pleural effusion by less than 50% or even increase of pleural effusion by less than 25%; progressive disease (PD) referred to an increase in pleural effusion, as well as worsening condition. CR and PR were considered as effective responses. The KPS grading standard was used for assessment of life quality: comparing the status at six weeks after treatment with that before treatment, an increase in KPS by more than and equal to 10 points for more than 4 weeks indicated status improvement; an increase or reduction in KPS by less than 10 points indicated stable status; an reduction in KPS by more than and equal to 10 points indicated deterioration.

Statistical analysis

The data were analyzed by using SPSS13.0 software. Intergroup comparison was made using the χ^2-test. A P value of < 0.05 indicated significance.

Results

Therapeutic efficacy

In the combination group, 14 (82.35%) of the 17 patients showed effectiveness; in the single-agent group, 9 (50.00%) of the 18 patients showed effectiveness. The response rate was significantly higher in the combination group than in the single-agent group (χ^2 = 4.062, P< 0.05) (Table 1).

Table 1 Comparison of response rate between the two groups

Group	Number	CR	PR	SD	PD	RR(%)
Combined	17	8	6	2	1	82.35
Single-agent	18	6	3	5	4	50.00

CR, complet remission; PR, partial remission; SD, stable disease; PD, progressive disease; RR, remission rate.

Improvement on general status

The improvement of general status was observed in 11 (64.70%) patients in the combination group and in six (33.33%) patients in the single-agent group. The improvement rate was significantly higher in the combination group than in the single-agent group (χ^2 = 4.250, P< 0.05) (Table 2).

Adverse events

The main adverse events during treatment for both groups were fever, chest pain, nausea and vomiting, and leucopenia, which were relieved after symptomatic treatment. The occurrence rate of fever was significantly higher in the combination group than in the single-agent group (58.82% vs. 11.11%, χ^2= 8.834, P < 0.05). All fevers were self-limited and recovered after 36 h, with no signs of upper respiratory tract infection and local body signs. No significant difference was observed in the occurrence rates of chest pain, digestive tract reaction, leucopenia, and impaired liver/kidney functions between the two groups (Table 3).

Table 2 Evaluation of quality of life for patients in the two groups

Group	Number	Modification	Steady	Aggravation	Modification rate(%)
Combined	17	11	5	1	64.70
Single-agent	18	6	7	5	33.33

Table 3 Comparison of the toxicities between the two groups

Toxicity	Combined group (number)	Single-agent group (number)	P
Total	17	18	–
Fever	10	2	0.003
Stethalgia	2	3	0.679
Nausea/Vomiting	5	7	0.555
Leukopenia	3	4	0.753
Hepatic insufficiency	0	0	–
Renal insufficiency	0	1	1.000

Discussion

Malignant pleural effusion is a common complication of lung cancer at progressive stage and is an indication of local advanced lung cancer.[1] The underlying mechanisms mainly include follows: 1) increase in capillary permeability; 2) swollen mediasternal lymph nodes that impede the of lymphatic fluid and blood reflux; 3) secretion or release of protein factors by tumor cells.[2] Uncontrolled malignant pleural effusion leads to chest pain, cough, racing heart, and dyspnea, which could affect life quality and even shorten survival time. Therefore, effective control of malignant pleural effusion plays an important role in comprehensive treatment for advanced tumors. The treatments for malignant pleural effusion include systemic and local therapy. Systemic treatment usually cannot effectively remove pleural effusion, while simple puncture drainage can only temporarily relieve symptoms because more effusion will occur. Currently, intracavity drug administration is mainly proposed, which has obvious pharmacokinetic advantage and can directly act on the pleural membrane, and the drugs can be absorbed through the membrane into circulation to reach tumor tissues, where it can have an effect of "double-edged sword".

The selected vector for rAd-p53 came from DNA of type 5 human adenovirus with the weakest pathogenicity. It is the first generation viral vector. rAd-p53 was constructed by gene recombination after deleting regions of E1A and E1B in the first generation type-5 adenovirus DJM17.[3] Its mechanisms are as follows:[4,5] 1) rAd-p53 induces cell cycle arrest and programmed death of tumor cells; 2) the introduction of wild-type p53 gene could increase the effects of chemotherapy and radiotherapy on tumor cells; 3) rAd-p53 inhibits the expression of vascular epidermal growth factor (VEGF) gene and multidrug-resistant genes, and causes apoptosis in tumor cells; 4) rAd-p53 stimulates anti-tumor immunity in body, leading to aggregation of immunological cells in tumor; 5) p53 protein could kill tumor cells by cell transduction, regulation of immune system, and induction of "bystander effect". Currently, DDP is the most commonly used cell cycle-unspecific broad-spectrum anti-tumor medicine, with well hydrosolubility and can be used locally or systemically. Local administration of DDP can maintain a relatively high concentration in local region with a low local clearance rate, and can directly eliminate tumor cells in different phases of cell cycle (the peak value of concentration and the sub-area of concentration-time curve for DDP in the thoracic cavity are 10 to 20 times of the values in serum).[6] In recent years, many researchers reported effective rate of 45%–67% for DDP used alone.[7] In this study, the effective rate for thoracic infusion of DDP alone was 50%, which was in accordance to other reports.

The study showed that the effective rate of the combination group was significantly higher than the single-agent group ($P<$ 0.05). This was possibly because rAd-p53 could increase sensitivity of lung cancer to DDP and it would not be affected by intrinsic p53.[8,9] Comparing with the single-agent group, 10 patients in the combination group developed low fever after injection of rAd-p53, but they were self-limiting and recovered in 36 h after symptomatic treatment. It was possibly due to the immune response induced by rAd-p53. Oral administration of Apamide in 30 min before rAd-p53 administration could alleviate fever. It was usually hard for drainage after two pleural infusions. If the percussion continued to be dull sounded and the respiratory sound was weak, the possibility of formation of capsulated pleural effusion in the thoracic cavity instead of complete removal of pleural effusion should be considered. Color ultrasonic examination could confirm the property of pleural effusion. Early injection of urokinase (100 000 units) and NS (20 mL) into the thoracic cavity is required for capsulated pleural effusion, the patient would then be required to perform frequent shift of body position afterward, effusion drainage could be performed 24 h later and repeated until pleural effusion was completely drained.[10]

Overall, gene therapy with rAd-p53 in combination with DDP yields good therapeutic efficacy on malignant pleural effusion due to lung cancer. It can effectively control pleural effusion, boost immunity of patients and improve life quality. It is worth of further investigation for its clinical application.

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