Clinical study on sequential application of Kanglaite Injection (KLT) and thrombin in treating cancerous pleural effusion

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[ABSTRACT]  Purpose  To study the clinical effect of KLT and thrombin in sequential treatment of cancerous pleural effusion.  Method  40 patients with cancerous pleural effusion were grouped randomly into treatment group and control group. The treatment group was treated through closed thoracic drainage followed by sequential application of KLT and thrombin while the control group was treated by KLT alone after closed thoracic drainage.  Result  Treatment group: complete response (CR) 4 cases, partial response (PR) 13 cases, no change (NC) 3 cases, response rate (RR) 85%. Control group: CR 1 case, PR 10 cases, NC 9 cases, RR 55%. There was observable effect difference between the two groups (P<0.05). Karnofsky score in both groups were increased after treatment. Improving rate were 90% in treatment group and 60% in control group respectively with significant difference (P<0.05).  Conclusion  The sequential application of KLT and thrombin can efficiently control cancerous pleural effusion and improve QOL which is therefore more desirable than KLT single use.

[KEY WORDS]  Cancerous pleural effusion; KLT; Thrombin


Cancerous pleural effusion is the pleural invasion of malignant tumor which brings blockade, metastasis, and induces exudation increasing and/or venous blood or lymph backflow obstacles and further leads to the abnormal build-up of pleural cavity fluid and presents symptoms like dyspnea, chest pain, and cough [1]. Cancerous pleural effusion is classifies as development and recurrence of disease. It usually suggests poor prognosis and greatly affects QOL and survival time of patients. Today, the most often approach to treat middle or large amount of cancerous pleural effusion is using thoracentesis drainage and intrapleural cavity injection. Therefore, 20 cases of patients with cancerous pleural effusion were included in our trial to be treated through closed thoracic drainage followed by sequential application of KLT and thrombin since 1999. Another 20 cases treated with KLT alone after closed thoracic drainage were involved at the same time for control. Results as follows.

1. Clinical data
1.1 General data
Among 40 patients: male 27 cases, female 13 cases; age 33~76, average 58.6; lung adenocarcinoma 15 cases, lung squamous carcinoma 12 cases, breast cancer 6 cases, esophageal squamous
carcinoma 5 cases, no type 2 cases. X-ray, B-ultrasound, and CT scan suggested unilateral middle or large pleural effusion. Tumor cells were found at least once in the effusion. Bloody pleural effusion by naked eyes 29 cases. Karnofsky score $\geq 50$ in all cases and estimated survival $> 3$ months. No severe cardiac, hepatic or renal dysfunction. No chemotherapy, intrapleural cavity injection or closed thoracic drainage 1 month before inclusion into the treatment, diagnostic puncture excluded. Patients or their authorized relatives were informed consent. According to the random number table, patients were divided into treatment group and control group with 20 cases each.

1.2 Treatment method
The two groups took the single means of closed thoracic drainage. Patients took seat. Locate the puncture point at medaxillary line by B-ultrasound. Insert the double cavity central venous catheters from Arrow’s USA into the pleural cavity which was connected by an external one-off gastrointestinal negative pressure drain for continuous drainage. Control the draining speed $< 800$ml within the first 1 hour and 100-200ml/h afterwards until exhaust. Then intracavitary treatment respectively in treatment group and control group. Treatment group: catheterize the pleural cavity, inject KLT 100ml and 5% Lidocaine 5ml. Turn off the drainage tube after drug injection. The patients were requested to lie on bed, turning over once every 15 min for 2 hours, making the drug liquid well exposed to the pleural cavity. Turn on the drainage tube 4 hours later. Catheterize the pleural cavity, inject thrombin 3000IU + physiological saline (NC) 30ml + Lodocaine 5ml after liquid draining off. Bed rest. Timing body turn over in 2 hours. Turn on the drainage tube 4 hours later for liquid discharge. Observation for 72 hours and took B-ultrasound exam. Draw out the catheter if no observable pleural effusion was found. Otherwise, repeat liquid discharge and intracavitary drug injection. Upper limit for drug injection: 3 times. Control group: catheterize the pleural cavity, inject KLT 100ml and 5% Lidocaine 5ml. Others were the same with treatment group.

1.3 Standard for efficacy evaluation
1.3.1 Efficacy evaluation - pleural effusion
Based on WHO standard, complete response (CR): pleural effusion disappeared for over 4 weeks; Partial response (PR): pleural effusion decreased by 1/2 and maintained over 4 weeks; no change (NC): fail to achieve the above standard.

1.3.2 Quality of life
Evaluated by WHO Karnofsky (KPS) score, KPS increased$> 10$ after treatment as improved, decreased $> 10$ as reduced, less than 10 in increase or decrease as stable.

1.3.3 Adverse reaction
Comply with WHO “Criterion for toxic reactions of anti-neoplastic drugs”. Stage 0~IV.
1.4 Statistical method

$X^2$ test, t test and rank sum test were adopted.

2. Result

2.1 Efficacy to pleural effusion. See table 1.

Table 1: Comparison of pleural effusion

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>CR</th>
<th>PR</th>
<th>NC</th>
<th>RR/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group</td>
<td>20</td>
<td>4</td>
<td>13</td>
<td>3</td>
<td>85$^\circ$</td>
</tr>
<tr>
<td>Control group</td>
<td>20</td>
<td>1</td>
<td>10</td>
<td>9</td>
<td>55</td>
</tr>
</tbody>
</table>

Note: $^\circ$ compared with the control group, $P<0.05$.

2.2 Karnofsky score. See table 2.

Table 2: Comparison of KPS score

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Improved</th>
<th>Stable</th>
<th>Reduced</th>
<th>Improving rate/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group</td>
<td>20</td>
<td>18</td>
<td>1</td>
<td>1</td>
<td>90$^\circ$</td>
</tr>
<tr>
<td>Control group</td>
<td>20</td>
<td>12</td>
<td>5</td>
<td>3</td>
<td>60</td>
</tr>
</tbody>
</table>

Note: $^\circ$ compared with the control group, $P<0.05$.

2.3 Adverse reactions

No severe adverse reactions in neither group. No treatment related hemogram inhibition, hepato-renal functional impairment, pneumothorax, or anaphylactic shock. Only 2 cases of slight fever and 1 case of chest pain in treatment group; 1 case of slight fever and 2 cases of chest pain in control group. They were relieved after symptomatic treatment. No significant difference on adverse reactions between the two groups ($P>0.05$).

2.4 Survival time

Treatment group (11.27 ± 2.78) months and control group (9.55 ± 2.45) months with significant difference ($P<0.05$).

3. Discussion

Cancerous pleural effusion is the common clinical complication of malignant tumor which mainly presents as hemorrhage effusion that can seriously impact the QOL and survival of patients. A usual way to treat the effusion is thoracentesis drainage and intrapleural cavity drug injection. Historically, chemical agents like cisplatin and bleomycin and sclerosing agents like talc and tetracyclind were reported to bring severe side effects that were hard to bear$^{[2]}$. To find a safe, low toxic and effective treatment method is, therefore, much required.
KLT is a modern botanical anticancer drug extracted from traditional Chinese medicine Coix seed with the function of biphasic broad-spectrum anticancer. A large amount of domestic animal tests and clinical researches had proved [3-5] that KLT was major act on G2/M stage of tumor cell mitosis. Its pharmacological actions: inhibition of tumor cell proliferation, induction of tumor cells apoptosis, cytokine level regulation, reversal of multi-drug resistance, inhibition of neo-vascularization, and effects on gene expression of cancer cells. That is why KLT can inhibit tumor cells and control the development and metastasis of tumor.

Thrombin is an instant local hemostat that can promote the transformation of fibrinogen to fibrin and can be combined with other blood components to form blood clot and further leads to blood coagulation and hemorrhage blocking. In addition, thrombin facilitates mitosis of epithelial cells, accelerate wound healing and reduce local effusion and thereby control cancerous pleural effusion [6-8].

In our trial, we adopted closed thoracic sustainable drainage and sequential application of KLT + thrombin to treat the cancerous pleural effusion. Clinical results showed that RR by this method could reach to 85% while RR by KLT alone was only 55%. There was significant difference (P<0.05). Meanwhile, QOL improvement and mean survival time in treatment group both excelled that of the control group (P<0.05). Therefore, it is concluded that the sequential application has synergetic effects and can enhance response rate clinically. It’s better than KLT single use and has little adverse reactions.

The results in our trial suggest that the method of sequential treatment of KLT + thrombin to treat the cancerous pleural effusion was safe and low toxic. It is worth clinical expansion.

References

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