The application of Kanglaite Injection (KLT) combining with small-dose somatostatin in treating advanced hepatic carcinoma

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[Abstract] Objective: To evaluate the efficacy of small dose somatostatin with KLT in the treatment of hepatic carcinoma. Method: 162 patients with advanced hepatic carcinoma from 2003 to 2008 were divided into three groups. Treatment group: 66 patients were administrated small dose somatostatin and KLT. Control group I: 54 patients were administrated small dose somatostatin. Control group II: 42 patients were administrated chemotherapeutics. Results: Evaluate the efficacy after four cycles: there were no complete response (CR) and partial response (PR) in three groups. Treatment group: 40 cases of stable disease (SD) were 60.6%. Control group I: 28 cases of SD were 51.9%. Control group II: 2 cases of SD were 48%. The median survival time: Treatment group is 6.8 months, control group I and II are 6 months and 3 months respectively. Clinical effects: KPS was increased by 20 points; treatment group is 68.2%, 55.6% and 4% for control group I and II. Conclusion: The treatment of hepatic carcinoma with small dose somatostatin is efficient, but the effect of small dose somatostatin with KLT is better.

[Key words] Small dose somatostatin, Kanglaite, hepatic carcinoma

1. Material and method
1.1 General information
Choose indicators that have defined pathological diagnosis in nonrandom way to observe the size and morphogenesis of the focus through doing CT and B-mode ultrasound. Analyze liver function, renal function, AFP testing value in the perspective of hematology and the expected survival time of the subjects must be more than three months. KPS ≥ 50 and the age shall be 30-70. After the signature of informed consent form by the subjects and their families, they are enrolled into the trial. Among 162 subjects, 66 subjects are chosen into treatment group, 54 subjects and 42 subjects are entered into control group I and control group II respectively according to their financial status and individual willingness.

1.2 Treatment regimen
Treatment group: Octreotide: 100µg Sc q8h, KLT: 100ml iv gtt qd, d1-d20, repeat the application 10 days after the treatment. The application wouldn’t stop until there is evidence that can prove the tumor is relieved.
Control group I: Apply Octreotide 100µg Sc q8h until the subject asks to stop or died. Control group II: 5-FU 500mg iv gtt d1-5, Mitomycin 8mg iv d1, Cisplatin 20mg iv gtt d1-5, repeat every 21 days.

1.3 Criteria for assessment
1.3.1 Clinical effect
According to the standard for short-term clinical effect of antitumor drug drafted by WHO, it can be classified as CR, PR, MR and SD. Assess clinical effect once every two months after drug application according to the standard.

1.3.2 Clinical benefit
Make an assessment basing on pain, behavior state and weight change. 1) Pain: Positive: decreased dosage of analgesics ≥50% and pain relief ≥50%; Negative: other results. 2) Behavior state: Positive: after treatment, KPS increased by ≥20 and last for ≥4 weeks; Negative: KPS decreased by ≥20 comparing with that of before treatment and last for ≥4 weeks; Stable: Other results. 3) Weight change: Positive: After treatment, body weight increased by ≥7% (apart from the weight of fluid accumulation in exocoeloma) and last for ≥4 weeks; Non-positive: other results.

1.3.3 Toxicity reaction
Observe and assess it according to standard for indications and classifications of antitumor drug acute and subacute toxicity identified by WHO.

1.4 Statistical processing
Apply SPSS predictive analytics software to treat immunological indicators before and after treatment and perform uniformity test of error variance to treat changed information. Apply t to test significant difference in average among groups of uniformity of error variance and examine the group of heterogeneity of variance, and apply matched t to check comparison on mean among groups.

2. Result
2.1 Clinical effect
Within 4 months (evaluation for 2 times), disease control rate: 60.6% for treatment group (40 cases SD, 26 cases PD); 51.9% for control group I (28 cases SD, 26 cases PD); 4.8% for control group II (2 cases SD, 40 cases PD); Time to Progression (TTP): 2.7 months for treatment group, 2.2 months and 0.5 month for control group I and II respectively; median survival period:
6.8 months for treatment group of which 7 cases exceed 24 months; 6 months and 3 months for control groups I and II separately.

### 2.2 Clinical benefit

The assessment for clinical benefit is made within 4 months (evaluation for two times). Treatment Group: Among 58 cases, class I and II pain of 20 cases disappeared, 8 cases relieved from class III to class II, 6 cases relieved from class IV to class II, and the positive rate for pain relieving is 58.6%; 51 cases have improvements in medical condition and quality of life, accounting for 77.3%. KPS of 45 cases increased by 20 points and positive rate of behavior state is 68.2%. The weight of 25 cases increased by more than 7% and ascites disappeared, and positive rate of weight change is 37.9%. Control group I: Among 42 cases, class I and II pain of 18 cases disappeared, 6 cases relieved from class III to class II, 5 cases relieved from class IV to class II and the positive rate for pain relieving is 69.0%; 39 cases have improvements in medical condition and quality of life, accounting for 72.2%. KPS of 30 cases increased by 20 points and positive rate of behavior state is 55.6%. The weight of 18 cases increased by more than 7% and ascites disappeared, and positive rate of weight change is 33.3%. Control group II: Among 38 cases, class I and II pain of 1 cases disappeared, 2 cases relieved from class III to class II, 3 cases relieved from class IV to class II and the positive rate for pain relieving is 15.8%; 39 cases have improvements in medical condition and quality of life, accounting for 72.2%. KPS of 2 cases increased by 20 points and positive rate of behavior state is 4.8%. There is no one in this group whose body weight increased and ascites disappeared and there is no positive rate for weight change.

### 2.3 Serum tumor maker

Within four months (evaluate for two times), AFP titrate decreased by more than 50%: 4 cases, more than 25%: 8 cases, no change: 18 cases and increased by more than 25%: 36 cases. Control group I: AFP titrate decreased by more than 50%: 3 cases, more than 25%: 6 cases, no change: 12 cases, increased by more than 25%: 3 cases. Control group II: AFP titrate increased by more than 50%: 1 case, more than 25%: 3 cases, no change: 4 cases and increased by more than 25%: 34 cases.

### 2.4 T lymphocyte subsets

The assessment for T lymphocyte subsets is made within 4 months (evaluation for two times). Treatment group: after treatment of T lymphocyte subsets, CD3, CD4, CD8 and CD4/CD8 value have increased significantly and the difference has its significance (P<0.05) (see Tab.1)
### Tab.1 Treatment group: Changes of T lymphocyte subsets and NK cell activity before and after treatment (x±s%)

<table>
<thead>
<tr>
<th></th>
<th>CD3</th>
<th>CD4</th>
<th>CD8</th>
<th>CD4/CD8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>37.55±8.98</td>
<td>27.74±9.56</td>
<td>25.12±7.31</td>
<td>1.10±0.28</td>
</tr>
<tr>
<td>After</td>
<td>46.12±10.69*</td>
<td>31.47±10.33*</td>
<td>22.02±7.46*</td>
<td>1.43±0.55*</td>
</tr>
</tbody>
</table>

Note: *P<0.05

Control group I: after treatment of T lymphocyte subsets, CD3, CD4, CD8 and CD4/CD8 value have no differences statistically. (See Tab.2)

### Tab.2 Control group I: Changes of T lymphocyte subsets and NK cell activity before and after treatment (x±s%)

<table>
<thead>
<tr>
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<th>CD3</th>
<th>CD4</th>
<th>CD8</th>
<th>CD4/CD8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>38.42±10.20</td>
<td>26.45±9.20</td>
<td>24.21±8.21</td>
<td>1.09±0.41</td>
</tr>
<tr>
<td>After</td>
<td>39.88±11.40</td>
<td>27.42±11.20</td>
<td>25.24±7.12</td>
<td>1.08±0.68</td>
</tr>
</tbody>
</table>

Note: *P>0.05

Control group II: after treatment of T lymphocyte subsets, CD3, CD4, CD8 and CD4/CD8 value have decreased significantly and the difference has statistic significance. (See Tab. 3)

### Tab.3 Control group II: Changes of T lymphocyte subsets and NK cell activity before and after treatment (x±s%)

<table>
<thead>
<tr>
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<th>CD3</th>
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<th>CD8</th>
<th>CD4/CD8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>37.12±10.20</td>
<td>26.47±10.43</td>
<td>25.12±9.66</td>
<td>1.05±0.55</td>
</tr>
<tr>
<td>After</td>
<td>23.55±7.78*</td>
<td>18.24±8.26*</td>
<td>42.12±10.34*</td>
<td>0.43±0.28*</td>
</tr>
</tbody>
</table>

Note: *P>0.05

### 2.5 Toxicity reaction

Toxicity reaction includes nausea and vomit. Treatment group: class I 11 cases, class II 6 cases, class III 0 case, class IV 0 case; control group I: class I 9 cases, class II 8 cases, class III 0 case, class IV 0 case; control group II: class I 6cases, class II 14 cases, class III 16 cases, class IV 6 cases. Besides, bone marrow suppression is also a symptom of toxicity reaction and it has not appeared in treatment group and control group I. Control group II: class I 5 cases, class II 8 cases, class III 18 cases and class IV 11 cases.

### 3. Discussion
According to the reports home and abroad in recent ten years, somatostatin induces mitosis that can treat tumors and have effects on malignant tumors with endocrine function [1-3]. Published in 1998 reported that Kouroumalis got biopsy liver through liver puncture for test and the result confirmed that a certain number of somatostatin acceptors are existed in liver organ of liver cancer patient. Applying large volume (500-1000µg/d) of somatostatin in treating advanced liver cancer patient can decrease AFP level significantly and extends survival time. Bulletin of Chinese Cancer and Chinese Journal of Hepatobiliary Surgery in 2000 reported the basic study on Octreotide inhibiting growth of liver cell and inducing apoptosis and discussion on Octreotide inhibiting growth mechanism of liver cell.

Octreotide, somatostatin analog, is synthesized in vitro. Comparing with Stilamin, Octreotide has stronger effects, longer half-life of plasma and effecting time and be used more conveniently. Octreotide can decrease the activity of MAPK through acceptor-2 and -3 to disturb cell cycle, have cells stopped in resting stage and inhibit liver cell proliferation [4-5]. Dimitrou lopoulos et al injected placebo or Octreotide for 127 cases of HCC patients randomly. The result indicated that blood, biological and chemical indicators improved in treatment group, AFP level were decreased, albumin was raised, the average median survival period was extended remarkably and the accumulated survival rate was raised. Therefore, Octreotide is highly relevant to treat HCC [6-8].

TCM treatment is very traditional in China, which enjoys identified features and is recognized by international scholars gradually. The features of TCM in treating tumors lie in the entirety, which can improve clinical signs and quality of life of the patients. KLT, extracted from coix seed that is defined as TCM, is a kind of emulsion for injection, which had a broad spectrum of antitumor action, inhibits cell proliferation, induces cell apoptosis, adjusts cytokine level, strengthens immunity function, provides high-energy nutrition and plays a role in anti-metastasis [9-10].

The study titled by applying small-dose somatostatin combining with KLT and applying small-dose somatostatin in treating advanced liver cancer was designed and practiced according to fore-mentioned theories. Result: The four-month clinical effects and median survival period are apparently more positive in group of applying small-dose somatostatin combining with KLT and applying small-dose somatostatin than that of group of applying chemotherapy purely. Besides, for the group applying small-dose somatostatin combining with KLT, the level of AFP titrate was decreased obviously and maintaining rate was high. After the treatment of T lymphocyte subsets, CD3, CD4, CD8 and CD4/CD8 value are increased apparently before and after the administration and the difference has significance. The
strengthening of T lymphocyte activity means the strengthening of antitumor capability. Patients’ condition was improved and clinical benefit concluded that positive rate of pain relief, behavior state and weight change are all higher than that of group without using KLT. There is no toxicity reaction. Tumor growth was inhibited, life of quality was improved and patients’ survival period was extended apparently by applying somatostatin combining with KLT. Therefore, applying somatostatin combining with KLT has effects on treating advanced liver cancer clinically and better clinical benefits.

References


