Safety and efficacy of GP96 autoimmune therapy in patients with hepatocellular carcinoma - A prospective single-arm clinical trial in China

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Background: Hepatocellular carcinoma is one of the most common malignant tumors in the world. Surgical resection is an effective way for patients to obtain good prognosis, however patients with hepatocellular carcinoma are prone to have early recurrence or metastasis. Unfortunately, up to now, there is no widely accepted effective adjuvant therapy for patients with hepatocellular carcinoma after surgery. The heat shock protein GP96 autoimmune therapy is a tumor-specific immunotherapy with great potential as the adjuvant therapy for patients with hepatocellular carcinoma. Therefore, our study intends to investigate the safety and efficacy of GP96 autoimmune therapy on the patients with hepatocellular carcinoma after surgical treatment.

Methods: From April 2013 to January 2015, 20 patients with hepatocellular carcinoma were treated with GP96 immunotherapy postoperatively in Cancer Hospital, Chinese Academy of Medical Sciences. Their clinicopathological and immunological features were analyzed and the prognosis was compared to that of 460 patients who received merely surgery in the same period with propensity score matching analysis.

Results:
1. General information: There were 20 patients in GP96 group, including 18 males and 2 females, with a median age of 54 years (range, 29-74). The number of patients at TNM stage I, II, III, IV were 11, 5, 3 and 1, respectively. The median follow-up time was 35.0 months (23.0-42.0).

2. Related Side Effects: Grade I adverse reactions occurred in 6 patients: 2 cases of low-grade fever, 2 cases of flu-like symptoms, 1 case of slight increase in blood pressure and 1 case of weakness, which all disappeared on their own.

3. Immunological Results: Autologous tumor-specific T cell response was significantly enhanced in GP96 group ($P <0.01$), with an average increase of $6.1 \pm 2.9$ times (autologous gp96 stimulation) or $3.7 \pm 2.1$ times (tumor antigen stimulation); After immunotherapy, the proportion of Central Memory T cells (Tcm) increased in peripheral blood (however $P>0.05$), and the proportion of Effective Memory T cells (Tem) did not increase significantly.

4. Patients outcome: 40 cases were screened out as the control group from 460 simple operation group, using propensity score matching analysis. The analysis showed that the 1, 2, 3-year OS was 100%, 100% and 93.8%, respectively, in the GP96 group compared with 95.0%, 82.5% and 74.0% in the control group. ($P = 0.078$). The DFS of GP96 group at 1, 2 and 3 years were 85.0%, 75.0% and 62.3% respectively, which was significantly better than those of the control group (80.0%, 45.0% and 27.4%, $p = 0.034$).

Conclusion: GP96 autoimmune therapy is a safe treatment, which may help to improve the immune status of patients with hepatocellular carcinoma and prevent recurrence.

Key words: Hepatocellular carcinoma, GP96, autoimmune therapy

Table 1. 1, 2, 3-year OS and RFS of GP96 group and control group

<table>
<thead>
<tr>
<th>Group</th>
<th>1y</th>
<th>2y</th>
<th>3y</th>
<th>1y</th>
<th>2y</th>
<th>3y</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP96</td>
<td>100%</td>
<td>100%</td>
<td>93.8%</td>
<td>85.0%</td>
<td>75.0%</td>
<td>62.3%</td>
</tr>
<tr>
<td>Control</td>
<td>95.0%</td>
<td>82.5%</td>
<td>74.0%</td>
<td>80.0%</td>
<td>45.0%</td>
<td>27.4%</td>
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Figure 1. OS and RFS between GP96 group and control group

Figure 2. Flow chart of the clinical trial

Figure 3. A. Autologous tumor-specific T cell response with gp96 stimulation. B. Autologous tumor-specific T cell response with tumor antigen stimulation.

Focus on early screening, surgical treatment and immunotherapy for hepatocellular carcinoma and colorectal carcinoma with liver metastases

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