Clinical Observation on Kanglaite Injection Combined with Small-dose of Cisplatin and 5-FU in the Treatment of Advanced Pancreatic Cancer

Li Qingshan, Gao Xuhong, Liu Lanfang

Abstract: Objective: To evaluate effectiveness, toxic and side effects of KLT Injection combined with small-dose of DDP and 5-FU in the treatment of pancreatic cancer. Methods: Chemotherapy regimen: KLT 100ml, iv drip, d1~d20, with an interval of 8 days. 5-FU 320mg/m².d, infusion time 8h, for 2 consecutive weeks. DDP 5mg/m².d, 5 times per week for 2 consecutive weeks, with an interval of 2 weeks, the treatment was continued for two treatment courses then performed the evaluation of therapeutic effect. Results: Among 12 cases of advanced pancreatic cancer patients, PR 2 cases, SD 7 cases, PD 3 cases, overall effective rate 16.67%, 7 cases got pain relieved, performance status (Karnofsky scale)score or body weight increased, clinical beneficial rate 58.33%. After the treatment the values of NK, CD3, CD4, CD4/CD8 were apparently increased. Major toxic and side effects were mild hematologic and digestive tract reactions. Conclusion: KLT Injection combined with small-dose of DDP and 5-FU in the treatment of pancreatic cancer could raise patient's remission rate and clinical beneficial response rate, while toxic and side effects were still tolerable.

Key words: Pancreatic tumor; KLT Injection; 5-FU; Cisplatin; Chemotherapy

Pancreatic cancer is a commonly occurred highly malignant digestive tract tumor, its incidence has risen increasingly year after year, quite few of them were diagnosed at early stage, and 75% of them have been at their late stage when diagnosed. Currently no satisfactory results have been obtained from existing various therapeutic approaches, we are lacking of effective drugs, prognosis of the treatment is therefore very poor, seeking new treatment methods is one of important clinical topics. From March 1999 to September 2002, the authors applied KLT Injection combined with small-dose of DDP and 5-FU (KFP regimen) in the treatment of pancreatic cancer and have obtained rather good short-term therapeutic results, which are now reported as follows.

1. Materials and Methods

1.1 Clinical data

Among 12 cases in the group, male 8 cases, female 4 cases; Age 45~74, Mean age 56. All the cases were confirmed as pancreatic cancer by CT, MRI or cytological examination, of which the cancer located at pancreatic head 6 cases, at pancreatic tail 4 cases, at whole pancreas 2 cases; Stage III 7 cases, Stage IV 5 cases; Karnofsky score 40~70 points, Median 60 points, all the cases were treated for the 1st time and without surgical treatment. The results of blood routine, hepatic and renal functions, and ECG examinations before treatment were normal, and without contraindications for chemotherapy.

1.2 Treatment methods
KLT Injection 100ml iv drip, d1~d20, with an interval of 8 days, 5-FU 320mg/m².d, infusion time 8h, for 2 consecutive weeks, DDP 5mg/m².d, 5 times per week, for 2 consecutive weeks, with an interval of 2 weeks, the treatment was continued for two treatment courses then performed the evaluation of efficacy.

1.3 Observation indexes

Changes of tumor size, body weight, health conditions, immunologic function, cardiac, hepatic and renal functions, and hematogram after the treatment were mainly observed. Mophologic and imaginologic changes (CT or MRI) before and after the treatment were re-checked monthly. Pain evaluation: Pain severity was assessed according to a Number Rating System (NRS), grade 1~3: mild pain, grade 4~7: moderate pain, grade 8~10: severe pain. Performance Status: The score was estimated monthly before and after the treatment based on Karnofsky scale. Body Weight: The body weight was weighed monthly before and after the treatment. Immunologic function and hepatic and renal functions: NK cell activity, T-lymphocytes subsets (CD3, CD4, CD8, CD4/CD8) were examined monthly before and after the treatment. Blood routine was re-checked 1~2 times a week. Hepatic and renal functions, ECG were re-examined monthly before and after the treatment, the adverse reactions after chemotherapy were recorded in detail.

1.4 Efficacy evaluation

1.4.1 Objective efficacy

In accordance with the General Criteria for Assessment of Efficacy promulgated by WHO in 1981, efficacy is divided into four grades, i.e. CR, PR, SD, and PD.

1.4.2 Clinical Beneficial Response (CBR)

After the end of treatment course, the therapeutic results were assessed by comparing pain, performance status, and body weight before and after the treatment. Assessment of performance status: Karnofsky scale was applied and a score increase of 20 points was assessed to be positive, and a decrease of > 20 points was assessed to be negative, while an increase or decrease of < 20 points was assessed to be stable. Change of body weight (BD): An increase of 7% was assessed to be positive, and a decrease of 7% was assessed to be negative, while an increase or decrease of < 7% was assessed to be stable. The sustained time of any above-mentioned item surpassing 4 weeks and without deterioration of other criteria can be assessed to be a clinical benefited person.

1.4.3 Criteria for judging toxicity

Toxicity can be classified into Grade I, II, III, IV.
1.5 Statistical process

The immunologic indexes before and after the treatment could be expressed with a mean ± standard deviation ($\overline{X} \pm S$), T-test was adopted before and after the treatment.

2. Results of Treatment

2.1 Therapeutic effect

No complete remission case was observed among 12 cases advance pancreatic cancer, PR 2 cases, SD 7 cases, PD 3 cases, overall effective rate 16.67%. Among the 12 cases their survival time was 3~14 months, and their median survival time 6 months.

2.2 Clinical beneficial response

Of the 12 cases, pain relieved, performance status score improved or gain weight 7 cases, all the 3 items improved 1 case, two items improved 3 cases, only one item improved 3 cases, clinical beneficial response rate 58.33%. Of the 10 cases who had pain, one case whose mild pain disappeared, another case whose moderate pain was relieved to mild pain, two cases whose severe pain was relieved to moderate pain, pain remission rate 40%. As for patient’s performance status, 5 cases increased by 20 points, negative 2 cases, stable 4 cases, performance status score positive rate 41.67%. 3 cases whose body weight increased by over 7%.

2.3 Changes of immunological function before and after the treatment

After the treatment the values of NK, CD3, CD4, CD4/CD8 were markedly increased, and had significant difference as compared with before the treatment (see Table I).

<table>
<thead>
<tr>
<th>Item</th>
<th>CD3 (%)</th>
<th>CD4 (%)</th>
<th>CD8 (%)</th>
<th>CD4/CD8</th>
<th>NK (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>42.42±9.56</td>
<td>25.05±10.25</td>
<td>20.20±9.67</td>
<td>1.24±0.30</td>
<td>21.67±3.28</td>
</tr>
<tr>
<td>After treatment</td>
<td>50.34±10.26</td>
<td>35.67±11.6</td>
<td>21.07±8.97</td>
<td>1.67±0.24</td>
<td>25.56±2.87</td>
</tr>
<tr>
<td>t value</td>
<td>3.62</td>
<td>4.11</td>
<td>1.33</td>
<td>3.15</td>
<td>2.12</td>
</tr>
<tr>
<td>P value</td>
<td>&lt; 0.01</td>
<td>&lt; 0.01</td>
<td>&gt; 0.05</td>
<td>&lt; 0.01</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

2.4 Toxic and side effects

After KFP regimen treatment leukopenia has occurred to various extent in the patients, part of them had mild digestive tract reactions, phlebitis appeared in four cases. No hepatic and renal impairment and abnormal ECG observed in all the cases. None of them discontinued the treatment due to chemotherapeutic reactions (see Table II).
Table II. Main short-term toxic and side effects of KFP regimen

<table>
<thead>
<tr>
<th>Toxic and side effects</th>
<th>0</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>8</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>33.3</td>
</tr>
<tr>
<td>Hb ↓</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Platelets ↓</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Nausea &amp; vomiting</td>
<td>6</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>50.0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>41.7</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>8</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>33.3</td>
</tr>
<tr>
<td>Alopecia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

3. Discussion

Surgery is the only effective means for treating pancreatic cancer, but the resectable cancer accounts merely for 15% of the patients, and the results of chemotherapy and radiotherapy haven’t been satisfactory. Most of chemotherapeutic agents are dosage-relying drug and high-dose chemotherapy has become the clinical hot spot, this has inevitably brought a high-efficient and high-toxicity phenomenon to patients. The research on low-dose DDP and 5-FU has provided a new idea and approach to tumor’s chemotherapy. Low-dose DDP can prevent methionine from entering into the cells by combining the methionine transferring protein on cell’s membrane thus enhancing anabolism of methionine, which is synthesized from homotypic cysteine within the cells, the methionine synthetase activity is enhanced thus cativating the folic acid metabolic system and increasing 5,10,CH₂F₄ in the cells and extending 5-FU’s inhibition time on TS, and therefore the combination of triple complex is increased that indirectly destroys cell’s DNA synthesis\(^1\). There was another report in the literature, DDP is the modifier of 5-FU in EP regimen, on the contrary, 5-FU can also strengthen DDP’s modifying action\(^2\). Among our 12 cases of advanced pancreatic cancer, PR 2 cases, overall effective rate 16.67%, survival period 3~14 months, median survival period 6 months, this is similar to what had been reported abroad\(^3\).

Kanglaite Injection is an anti-cancer drug prepared from a TCM herb-Coix seed by extracting its anti-cancer components and processed into a dosage form-emulsion, which has anti-cancer effect as well as immunologic function-enhancing effect. Clinical practice has verified that its inhibitory and killing effect on cancer cells is mainly passed through arresting phase G2 and M cells, leading to decreasing percentage of phase S cells, reducing mitosis and inhibiting the proliferation of tumor cells thus leading to the apoptosis of the affected cells. A synergistic effect can be achieved when it is in combination with other anticancer drugs, at the same time, it reduces the adverse reactions of radio- and chemo-therapies, it not only supplies high-energy nutrients, but also fights against cachexia\(^4\). In this group the values of CD3, CD4, and CD4/CD8 after treatment were increased compared with those before treatment, the difference between them was significant. Among the 12 cases, the clinical beneficial reaction rate was 58.33%, pain remission rate 40%, performance status score

\(^1\) Reference

\(^2\) Reference

\(^3\) Reference

\(^4\) Reference
positive rate 41.67%, body weight change positive rate 25%, indicating KLT significantly improved the survival quality of advanced cancer patients.

In this paper the authors adopted KLT combined with FP regimen in the treatment, no treatment was required for its side effects. The frequently seen side effects such as phlebitis, which was avoidable by means of deep vein continuous infusion; stomatitis and diarrhea was preventable through oral administration of vitamins and intestinal mucosa protecting agent; no renal function impairment has been observed owing to the application of small dosage of cisplatin.

In our treatment we used KLT combined with low-dosage FP regimen, since the daily dose of 5-FU and DDP was low, not only the efficacy was enhanced, but the toxic and side effects were reduced simultaneously, and the quality of life improved, hence, this treatment is most suitable for elderly and feeble advanced cancer patients.

References