Original Article

The clinical efficacy of S-1 combined with gemcitabine in senile patients with advanced pancreatic cancer and the drugs’ effects on quality of life

Yuqiang Liu1*, Yu Wang2*, Chunxia Hou1

Departments of 1Pharmacy, 2Oncology, Changzhi People’s Hospital, Changzhi 046000, Shanxi, China. *Equal contributors and co-first authors.

Received October 29, 2019; Accepted December 17, 2019; Epub March 15, 2020; Published March 30, 2020

Abstract: Objective: This study aimed to explore the clinical efficacy of S-1 combined with gemcitabine in senile patients with advanced pancreatic cancer, and the drugs’ effects on quality of life. Methods: 64 senile patients with advanced pancreatic cancer admitted to our hospital were retrospectively analyzed according to their clinicopathological characteristics and divided into a control group (n=32) and an observation group (n=32). After treatment with S-1, the control group was compared with the observation group which was treated with S-1 and gemcitabine in terms of clinical efficacy, serum natural killer T (NKT), Interferon-γ (IFN-γ), T cell subsets of immune function indexes (CD3+, CD4+ and CD8+), toxic reaction, quality of life (QOL), and survival time. Results: The observation group reported a higher effective rate of treatment than the control group (P<0.05), and the treatment resulted in the elevation of the NKT, IFN-γ, CD3+, CD4+, CD4+/CD8+, and QOL scores, and a reduction in CD8+ in both groups, after which, the NKT, IFN-γ, CD3+, CD4+, and CD4+/CD8+ levels were higher, and the CD8+ level was lower in the observation group compared with the control group (P<0.05). Without any statistical differences in the toxic reaction rate calculated based on the toxic reactions including neutropenia, afebrile and nausea/vomiting (P>0.05), the observation group had a longer median survival time, a median disease progression time, and a higher 1-year survival time rate than the control group (P<0.05). Conclusion: Considering, the combination of S-1 and gemcitabine compared with the application of S-1 alone, the combination of S-1 and gemcitabine can achieve a better efficacy, improve QOL, and extend the survival time of senile patients with advanced pancreatic cancer without additional adverse reactions. Those advantages are thought to be associated with the improved structures of the T-cell subsets and expressions of NKT and IFN-γ.

Keywords: Advanced pancreatic cancer, senility, S-1, gemcitabine, quality of life, immunologic function

Introduction

Pancreatic cancer is a highly malignant tumor that can be surgically resected in only 10% to 15% of patients, who also likely face a dreadful prognosis [1]. For patients with advanced pancreatic cancer who missed the opportunity for surgical treatment, first-line chemotherapy with gemcitabine is usually the drug of choice to extend their survival time and improve their QOL to a certain degree, but its effects are unsatisfactory [2, 3]. S-1 is a drug from the fluorouracil family and is usually applied in the treatment of tumors of the gastrointestinal tract, head, and neck due to its less toxic side effects [4, 5]. Relevant studies [6] have revealed that the combination of S-1 and gemcitabine in chemotherapy can elevate the survival rate and extend the median survival time of patients with advanced pancreatic cancer with less toxic reactions at or above grade III, and with a better tolerance in patients. In addition, S-1 is more acceptable to patients, as it is easy to use by oral administration [7]. However, there are few clinical studies on the application of S-1 combined with gemcitabine in senile patients with advanced pancreatic cancer. This study compared S-1 combined with gemcitabine in terms of the combination’s effects on QOL, clinical efficacy, immunologic function, QOL and survival rate in senile patients with advanced pancreatic cancer, in order to pro-
vide information on the selection of chemotherapy plans for senile patients.

Material and methods

Clinicopathological data

The clinicopathological data of the 64 senile patients with advanced pancreatic cancer admitted to our hospital were retrospectively analyzed. Inclusion criteria: Patients between 60 and 80 years old and expected to survive longer than 3 months, who met the diagnostic criteria of pancreatic cancer in the Guidelines to the Diagnosis and Treatment of Pancreatic Cancer and had not received chemotherapy in the last 3 months were included, and they provided their informed consents. Exclusion criteria: Some patients were excluded as they had other primary malignant tumors, endocrine system diseases, autoimmune diseases, dementia, or mental diseases concurrently or who had acute cardiovascular and cerebrovascular diseases in the last 6 months or who underwent a major operation in the last 3 months. The study was approved by the Medical Ethics Committee. The 64 patients were divided equally into the control group and the observation group. The control group included 20 males and 12 females, ranged in age from 60 to 79 with (67.37±9.63) years as the mean, whose BMI ranged from 18 to 24 kg/m$^2$ with (21.05±2.23) m$^2$ as the mean, an ECOG score from 0 to 1 with (0.52±0.11) as the mean, while in the observation group, the corresponding data were 22, 10, 62-77, (67.25±9.48) years, 18-25 kg/m$^2$, (21.08±2.26) m$^2$, 0~1 and (0.56±0.13). The 2 groups were not statistically different but comparable in their clinicopathological data (P>0.05).

Methods

The control group was orally administered S-1 capsules (Jiangsu Hengrui Medicine Co., Ltd., GYZZ H20100135, specification: 20 mg) twice a day at a dose of 40 mg/m$^2$ for 14 days ($d_{1-14}$). The observation group received a combination treatment of S-1 by oral administration twice a day at a dose of 40 mg/m$^2$ for 14 days and gemcitabine (Jiangsu Hansoh Pharma Group Co., Ltd., GYZZ H20030104, specification: 0.2 g) by intravenous drip once a day at a dose of 1000 mg/m$^2$ on the 1st, 8th, and 15th days. Both treatments consisted of 2 courses (3 weeks each).

Evaluation criteria

Evaluation criteria of the efficacy: complete response (CR): the original lesions have disappeared completely; partial response (PR): the original lesions are reduced by 50% or more but didn’t disappear, and no new lesions occurred; no change: the original lesions are reduced by less than 50% or expanded by less than 25%, and no new lesions developed; progressive disease (PD): new lesions developed or the original lesions expanded by 25% or more. Effective rate = (CR+PR)/n in the group × 100%.

Serum IFN-γ quantification: before and after the treatment, 3 ml blood was drawn from the fasting patients’ veins, centrifuged at 3000 r/min for 5 min, and tested for IFN-γ using ELISA with the test kits produced by the American R&D Company. The specific steps were as follows: the buffer solution was diluted to 10 μg/ml and added to the reaction wells at a volume of 0.1 ml. It was kept overnight at under 4°C, and then rinsed 3 times before the addition of 0.05 ml sample into the reaction wells for 1 h incubation at room temperature and rinsing. The enzyme labeled antibody was then added, and the mixture was incubated for 30 min at room temperature and rinsed again. Afterward, for the purpose of coloration, a substrate was added and incubated for 30 min at room temperature, and 0.05 ml of 2 M sulfuric acid was added to terminate the reaction. The optical density was read at a wavelength of 450 nm with an enzyme-labeled analyzer produced by Hamilton Medical, Switzerland to calculate the concentration.

Immunologic function detection: 2 ml of blood was drawn from the fasting patients’ veins and assayed for the NKT and T cell subsets (CD$^+$, CD$^+$, and CD$^+$) with a flow cytometer developed by the American company BD FACSVerse to calculate the CD$^+/CD^+$.

Toxic reactions: toxic reactions were evaluated according to the evaluation criteria for adverse reactions and events developed by the National Institutes of Health, United States Department of Health and Human Services in cooperation with the National Cancer Institute.

QOL evaluation: the patients were evaluated using QLQ-C30 which consists of 5 subscales for the functions of PF, RF, CF, EF and SF, and
The efficacy of tegafur combined with gemcitabine

The combination of S-1 and gemcitabine can reduce the levels of NKT and IFN-γ in senile patients with advanced pancreatic cancer

The combination of S-1 and gemcitabine can improve the immunologic function of senile patients with advanced pancreatic cancer

The combination of S-1 and gemcitabine can improve the QOL of senile patients with advanced pancreatic cancer

| Table 1. Comparison of the two groups in clinical efficacy [n (%)] |
|---|---|---|---|---|---|---|
| Group | n  | CR  | PR  | NC  | PD  | Effective Rate |
| Observation group | 32 | 10 (31.25) | 12 (37.50) | 7 (21.88) | 3 (9.37) | 22 (68.75) |
| Control group | 32 | 5 (15.62) | 8 (25.00) | 12 (37.50) | 7 (21.88) | 13 (40.63) |
| $\chi^2$ | 5.107 |
| P | 0.024 |

Figure 1. Comparison of the two groups in their NKT and IFN-γ levels ($\bar{X} \pm s$). Note: ***P<0.001 as compared with the conditions before treatment; ###P<0.001 as compared with the control group. NKT: natural killer T; IFN-γ: Interferon-γ.
The efficacy of tegafur combined with gemcitabine

achieved higher dimensional scores than the control group after treatment, though an elevation was reported in both groups (P<0.05), which indicated that the combination of S-1 and gemcitabine can improve the QOL in senile patients with advanced pancreatic cancer more effectively than the S-1 treatment alone (Figure 3).

The combination of S-1 and gemcitabine didn’t result in additional toxic reactions

The 2 groups had no statistical differences in terms of the incidence of toxic reactions such as neutropenia, aequocytosis, and nausea/vomiting (P>0.05), indicating that the combination of S-1 and gemcitabine will not increase toxic reactions with guaranteed clinical safety (Table 2).

The combination of S-1 and gemcitabine can significantly extend the survival of senile patients with advanced pancreatic cancer

The observation group exceeded the control group in terms of median survival time, median disease progression time, and 1-year survival rate (P<0.05), indicating that the combination of S-1 and gemcitabine can significantly extend the survival of senile patients with advanced pancreatic cancer, with an efficacy superior to S-1 treatment alone (Table 3).

Discussion

Pancreatic cancer is characterized by a high grade of malignancy, a high fatality rate, and a poor prognosis, with a mean survival time of about 6 months, a 5-year survival rate lower than 5%, and an incidence rate approaching mortality [8, 9]. In recent years, changes in dieting and living habits have resulted in an increasingly rising incidence of pancreatic cancer, which severely endangers our health. Though surgical resection is a possible therapeutic tool for pancreatic cancer, most patients have entered into the advanced stages and lost the best surgical opportunity when seeking a doctor’s advice. Patients with advanced pancreatic cancer have to mainly depend on chemotherapy with gemcitabine as the first-line standard chemotherapy plan, which, however, is not so satisfactory in its overall effects. Relevant studies [10] have revealed a total effective rate of 28%, a disease control rate of 69%, a PFS of 5.3 months, and a TS of 6.6 months in the 90 patients with advanced pancreatic cancer after chemotherapy with gemcitabine, lower than the results obtained from a combined chemotherapy plan with gemcitabine.

S-1 is a compound drug containing tegafur, gimeracil and oteracil potassium. Among the 3 ingredients, tegafur can be transformed into 5-Fu through hepatic activation, which further works on the S phase in the cell cycle to block the production of deoxyribonucleic acid and ribonucleic acid, and the reproduction of cancer cells for the purpose of killing tumors [11, 12]. Gimeracil is a dihydropyrimidine dehydrogenase inhibitor against 5-Fu decomposition to extend the effective drug duration (EDD) [13], while oteracil reacts with orotate phosphoribosyl transferase (OPRT) to prevent 5-Fu from acidification and inhibit the toxic reactions therefrom [14]. Gemcitabine is a cytosine nucleoside derivative that acts on tumors by producing metabolin to affect the G1/S phase of cells, inhibit the reproduction of tumor cells

Figure 2. Comparison of the two groups in immunologic function. Note: ***P<0.001 as compared with the conditions before treatment; ###P<0.001 as compared with the control group.
The efficacy of tegafur combined with gemcitabine

and ribonucleotide reductase, and reduce deoxynucleoside triphosphate [15, 16]. The study showed that the combination of S-1 and gemcitabine in senile patients with advanced pancreatic cancer can achieve a higher effective rate than the control group, but no marked difference was observed in the incidence of bone marrow arrest, gastrointestinal toxicity, or skin lesions, indicating that the combination of S-1 and gemcitabine was superior to the single administration of S-1 in terms of clinical efficacy, and without any additional adverse reactions. Such improvements shall be attributed to the synergy when the 2 drugs are given at the same time, in which, oteracil inhibited the toxic adverse reactions related to other ingredients in S-1 and gemcitabine, so no significant increase in toxic reactions was observed.

The development and progression of tumors are associated with various cell factors and immunologic dysfunction [17, 18]. NKT is a special T cell subset, and it can kill tumor cells according to some studies [19], while IFN-γ, in addition to activating a number of signal paths including activating the transcription factors (ATF) and MAPA, and inducing the growth, differentiation and apoptosis of cells [20], can also inhibit the division growth of cancer cells and accelerate their apoptosis, and biologically fight against tumors [21]. In patients with malignant tumors, CD3+, CD4+ and CD8+ were out of balance due to some factors secreted by tumors, resulting in immunologic dysfunction [22]. According to some studies, patients with malignant tumors are in an immunologic suppression status manifested as a reduced ca-

Table 2. Comparison of the two groups in toxic reactions [n (%)]

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Neutropenia</th>
<th>Afeucytosis</th>
<th>Nausea/vomiting</th>
<th>Anaemia</th>
<th>Erythra</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation Group</td>
<td>32</td>
<td>14 (43.75)</td>
<td>15 (46.88)</td>
<td>11 (34.38)</td>
<td>5 (15.63)</td>
<td>3 (93.75)</td>
</tr>
<tr>
<td>Control Group</td>
<td>32</td>
<td>12 (37.50)</td>
<td>11 (34.38)</td>
<td>9 (28.13)</td>
<td>3 (93.75)</td>
<td>1 (3.44)</td>
</tr>
<tr>
<td>χ²</td>
<td></td>
<td>0.259</td>
<td>1.036</td>
<td>0.290</td>
<td>0.142</td>
<td>0.267</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>0.611</td>
<td>0.309</td>
<td>0.590</td>
<td>0.450</td>
<td>0.302</td>
</tr>
</tbody>
</table>

Table 3. Comparison of the two groups in survival [n (%)]

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Median survival time (month)</th>
<th>Median disease progression time (month)</th>
<th>6-month survival rate (%)</th>
<th>1-year Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation Group</td>
<td>32</td>
<td>12 (95% CI=4-20)</td>
<td>7 (95% CI=2-18)</td>
<td>26 (81.25)</td>
<td>12 (37.50)</td>
</tr>
<tr>
<td>Control Group</td>
<td>32</td>
<td>10 (95% CI=2-26)</td>
<td>6 (95% CI=2-10)</td>
<td>20 (62.50)</td>
<td>6 (18.75)</td>
</tr>
<tr>
<td>χ²</td>
<td></td>
<td>5.732</td>
<td>5.438</td>
<td>2.783</td>
<td>4.560</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>0.003</td>
<td>0.005</td>
<td>0.095</td>
<td>0.033</td>
</tr>
</tbody>
</table>

Figure 3. Comparison between the 2 Groups for Quality of Life. Note: ***P<0.001 as compared with the conditions before treatment; ###P<0.001 as compared with the control group. PF: physical function; RF: role function; CF: cognitive function; EF: emotional function; SF: social function.
The efficacy of tegafur combined with gemcitabine

pacity of the immune system when killing cancer cells. As a result, tumors grow rapidly [23]. The results of the study indicated an elevation in NKT and IFN-γ, \( \text{CD}^+ \), \( \text{CD}^- \), and \( \text{CD}^+ / \text{CD}^- \), and a reduction in \( \text{CD}^+ \) in both groups after treatment, elevations which were more significant in the observation group, and which were consistent with the findings of previous studies [24]. Those results revealed that the combination of S-1 and gemcitabine in treating senile patients with pancreatic cancer can rectify the immunologic dysfunction, enhance the immunity, and improve the NKT and IFN-γ levels. Also, through the study it was learned that the treatment led to higher QOL scores in both groups, scores which were more significant in the observation group. In addition, the observation group surpassed the control group in terms of median survival time, median disease progression time, and 1-year survival time as found in similar studies [25], making it clear that the combination of S-1 and gemcitabine can extend the survival time and 1-year survival rate of senile patients with advanced pancreatic cancer and improve their quality of life. This is because the combination of S-1 and gemcitabine can better reinforce immunologic function, and therefore control disease progression and lengthen patients’ survival times.

In conclusion, the combination of S-1 and gemcitabine in treating senile patients with advanced pancreatic cancer can improve treatment efficacy and the patients’ quality of life and extend their survival times without additional adverse reactions. The efficacy was superior to the single administration of S-1 due to the possible improvements in the T-cell subset structure and the NKT and IFN-γ expressions.

Disclosure of conflict of interest

None.

Address correspondence to: Yuqiang Liu, Department of Pharmacy, Changzhi People’s Hospital, No. 502, Changxing Middle Road, Luzhou District, Changzhi 046000, Shanxi, China. Tel: +86-0355-2059055; E-mail: liuyq900@163.com

References


The efficacy of tegafur combined with gemcitabine


