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**S-1 plus gemcitabine chemotherapy followed by concurrent radiotherapy and maintenance therapy with S-1 for unresectable pancreatic cancer**

Ke qh *et al*. New treatment for pancreatic cancer

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**Abstract**

**AIM:** to investigate the feasibility and efficacy of combination of S-1 with gemcitabine and followed by oral S-1 with concurrent radiotherapy (intensity modulated radiotherapy, IMRT) and maintenance therapy with S-1for locally advanced pancreatic cancer.

**Methods:** patients had unresectable and locally advanced pancreatic cancer, without distant metastases, adequate organ and marrow functions, had an Eastern Cooperative Oncology Group performance status of 0-1, and no prior anticancer therapy. Initially received two cycles of chemotherapy, oral administration of S-1 40 mg/m2 twice daily from day 1 to day14 of a 21-d cycle, and consisting of 30-min intravenous infusions of gemcitabine 1000 mg/m2 on day 1 and day 8. Two weeks after the completion of chemotherapy, S-1 was administered orally with concurrent IMRT, oral administration of S-1 at a dose of 80 mg/m2 per day twice daily from day 1 to day 14 and from day 22 to day 35. A total radiation was concurrently delivered at dose of 50.4 Gy (1.8 Gy/d, 5 times per week, 28 fractions). One month after the completion of chemotherapy and radiotherapy, S1 was administered orally at a dose of 80 mg/m2 per day twice daily for 14 d, followed by a 14-d rest period. This cycle was repeated as maintenance therapy, until unacceptable toxicity or disease progression. Thirty-two patients were joined in this study. The median follow-up was 15.6 mo (about 8.6-32.3 mo).

**Results**: Thirty-two patients completed the scheduled course of chemotherapy. Thirty patients (93.8%) completed the scheduled course of chemoradiotherapy. Two patients gave up radiotherapy. The major toxic effects were nausea and leukopenia. There was no grade 4 toxicity or treatment-related death. According to the Response Evaluation Criteria in Solid Tumours criteria, the objective tumor response was partial response in 17 patients, about 53.1%, stable disease in 9, about 28.1%, and progressive disease in 6, about 18.8%. The median overall survival and median progression-free survival were 15.2 mo and 9.3 mo, respectively. The survival rates at 1 year and 2 years were 75% and 34.4%, respectively.

**Conclusion**: It is considered a well-tolerated, promising regimen that Combination of S-1 with gemcitabine and followed by oral S-1 with IMRT and maintenance therapy with S-1 alone in patients with locally advanced pancreatic cancer.

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**Key words:** Chemoradiotherapy; Radiosensitizer; S-1; Pancreatic cancer; CA19-9

**Core tip:** The article describes a study of combination of S-1 with gemcitabine S-1 followed by oral S-1 with concurrent radiotherapy and maintenance therapy with S-1 for locally advanced pancreatic cancer, it is considered a well-tolerated, promising and effective treatment for unresectable advanced pancreatic cancer.

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**INTRODUCTION**

The prognosis of pancreatic cancer (PC) patients remains very poor, with a 5-year survival rate less than 5% after diagnosis[1-4]. PC is one cancer of the leading causes of death worldwide.In most historical studies, for the patients with locally advanced PC, the median survival ranges from about 8 to 12 mo[5-8].

It is important that the order in which radiation and chemotherapy are given to the patients with locally advanced PC. 20% patients who received initial chemoradiation have been found immediate metastases after therapy[9,10]. Furthermore, the patients received initial chemoradiation maybe experience much more toxicities than the patients only received chemotherapy. Because of these toxicities, the subsequent chemotherapy that is needed to delay and/or prevent metastatic disease may be interfered.Therefore there is a good alternative approach to start with a few cycles of induction chemotherapy (2 to 4 cycles) and then to revalue the patients. The patients without distant metastases on restaging and have a good performance status, may be consolidated by chemoradiation. The alternative approach may make those patients to be benefit from chemoradiation, has shown to delay or prevent locoregional progression which could lead to duodenal obstruction or result in pain (involved celiac plexus). Some studies have also shown that when compared to chemotherapy alone, chemoradiation-based control of local progression can improve survival and prevent the development of metastatic disease[5,11].

Some current single phase Ⅱ studies have showed obvious increases in the median survival by targeted agents, radiosensitizers, and/or combination chemotherapy, during conjunction with radiation therapy and/or in the induction phase of treatment[12-15]. Just like, S-1 is a new oral fluoropyrimidine formulation that combines tegafur, 5-chloro-2,4-dihydroxypyridine (CDHP), and potassiumoxonate in a molar ratio of 1:0.4:1.

Sudo reported in his study that outcomes were promising, a 1-year survival rate of 70.6% and with a median OS of 16.8 mo and toxicity rates were acceptable (Grade 3-4),which S-1 was given concurrently with radiation (total dose 50.4 Gy) and followed with oral S-1 maintenance in patients with locally advanced PC[9].

Many modern studies have reported improvements in treatment related survival and toxicity[16-18], Which use aggressive induction therapy and/or dose escalated radiation therapy using SBRT, 3D conformal or IMRT.

**MATERIALS AND METHODS**

***Patient eligibility***

Entry patients were locally unresectable advanced pancreatic cancer which had cytologically or histologically confirmed. The patients estimated life expectancy 12 wk after study entry; were age 46–69 years; written informed consent;no evidence of distant metastasis; Karnofsky Performance Status 70–100 points; no earlier treatment for pancreatic cancer; adequate oral intake; adequate hepatic and renal function; adequate haematological function.

Exclusion criteria were active gastroduodenal ulcer; pleural effusion or ascites; watery diarrhoea;active infection; Some complication just like active concomitant malignancy; history of drug hypersensitivity; mental disorder;heart disease or renal disease; females of childbearing age unless using effective contraception;pregnant and lactating females.

For pretreatment staging, the chest and abdomen computed tomography were asked to exclude the presence of distant metastasis and to assess the local extension of the tumour. Tumor unresectability criteria of the computed tomography-based included tumor encasement of bilateral invasion of the portal vein, superior mesenteric artery,common hepatic artery, or the celiac trunk. Before treatment, all patients with obstructive jaundice underwent endoscopic retrograde biliary drainage or percutaneous transhepatic.

Patient characteristics

Thirty-two patients were joined in the study from March 2010 to December 2012 in the Oncology Hospital of Jingzhou, China. The patient，s characteristics are listed in Table 1. Karnofsky Performance Status was 80 in three (9.4%), 90 in 9 (28.1%), and 100 in 20 patients (62.5%). The median age was 55 years (range: 50–69). The median planning target volume was 255 cm3 (range: 149–398) and the median maximum tumour size was 36 mm (range: 24–57). Among the unresectable PCs,there were eleven patients invasion of the superior mesenteric artery, sixteen patients invasion of the celiac trunk, and five patients invasion of both regions.

***Treatment schedule***

About 32 patients received two cycles of induction chemotherapy, S-1 was administrated 40 mg/m2 twice daily from day 1 to day 14, gemcitabine was performed with 30-min intravenous infusions of 1000 mg/m2 on day 1 and day 8 of during a 21-d cycle.

After the induction chemotherapy finished about two weeks, the patients were treated with S-1 and concurrent radiation. S-1 was performed 80 mg/m2 from day 1 to day 14 and then from day 22 to day 35, orally twice daily on the day of irradiation during radiotherapy. One month after the completed chemoradiotherapy, S-1 was administered 80 mg/m2 per day twice daily for 14 d, then a 14 d rest period. The cycle was repeated as maintenance therapy until unacceptable toxicity or disease progression.

The intensity modulated radiotherapy (IMRT) technique was administered by three-dimensional treatment planning using 10 or 15 MV photons. The total dose was 50.4 Gy delivered in 28 fractions, about 5.5 wk. The area of solid macroscopic tumor that contrast enhancement on MR and CT-imaging and/or PET positive will be defined as the Gross Tumor Volume (GTV). The GTV plus a margin of at least 5 mm, including any areas of microscopic spread and the regional lymph nodes. will be defined as the Clinical Target Volume (CTV). The CTV plus a 10 mm margin in the craniocaudal direction and 5 mm margin in the lateral direction to account for daily set-up error and respiratory organ motion was defined as the planning target volume (PTV). The dose of the liver which received by 50% was limited to 30 Gy, the dose of both kidneys which received by 50% was limited to 20 Gy. The dose of spinal cord was maintained below 45 Gy.

***Evaluation***

All the eligible patients must be included in the toxicity and response evaluations. During chemotherapy, biochemistry tests, complete blood cell counts and Physical examination were assessed at least on day 1 and day 8 in each cycle. According to the Response Evaluation Criteria In Solid Tumors version 1.0, Objective tumor response was evaluated every 4–6 wk by magnetic resonance imaging or computed tomography. CA 19-9 (tumor marker carbohydrate antigen ) was measured every 4–6 wk too. In this study, the CR (the complete response), PR (partial response) and SD (stable disease) was required an interval of at least 4 wk to confirm the objective response. The interval that from the first documentation of response (CR or PR) to the first documentation of tumor progression was defined as the response duration. According to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0, adverse events were evaluated. Objective responses and adverse events was confirmed by an external review committee. From the date of treatment initiation to the date of censored at the last follow-up or death was calculated as overall survival (OS). From the date of the initiation of treatment until documented disease progression or death due to any cause was calculated as progression-free survival (PFS)

**RESULTS**

***Efficacy***

All of the patients were included in the response evaluation. Tumors criteria was partial response in 17 patients (53.1%), stable disease in 9 (28.1%), and progressive disease in 4 (12.5%). Only two patient (6.3%) could not evaluate the tumor response, because they went to another hospital to receive some other treatment. After the completion of the treatment, none of the patients' conditions improved to operable or resectable diseases. The serum CEA level was reduced by more than 50%, which relative to the pretreatment level in three of four (75%) patients who had a pretreatment level of 10 ng/ml or greater, and the serum CA19-9 level was reduced by more than 50%, which compared to the pretreatment level in 24 of 28 (85.7%) patients who had shown a pretreatment level of 100 U/ml or greater.At the time of analysis, 29 of the 32 patients had disease progression. The type of the disease progression was locoregional recurrence in three patients (9.38%), deterioration of general condition in four (12.5%) and distant metastases in 10 (31.3%). Median overall survival and median progression-free survival were 15.2 mo and 9.3 mo, respectively. The survival rates at 1 year and 2 years were 75% and 34.4%, respectively (Figure 1).

***Toxicity***

There were listed in Table 2 that the toxicities observed in the 32 enrolled patients. As acute nonhaematological toxicity, grade 3 AST elevation (two patient), grade 3 vomiting (four patient), and grade 3 anorexia and nausea (eight patients) and grade 3 haemorrhagic gastritis (one patient) were observed. As acute haematological toxicity, grades 4 toxicities were not observed and grade 3 neutropenia was observed in only two patient. We observed duodenal ulcer 7 mo after treatment in one patient as a late toxicity, but no other late toxicity occurred. No treatment-related deaths or other grades 3–4 nonhaematological toxicities occurred in the study. Because of grade 3 anorexia,the treatment was stopped in two patients, during the therapy they did not receive S-1 on day 3 and day 12. It was as high as 93.8% that the compliance rate of the patients taking S-1. There were two patients of the 32 who were enrolled this study had to abandon this treatment because of the progressive disease.

**DISCUSSION**

The prognosis of patients with locally advanced pancreatic adenocarcinoma is extremely poor. Because many patients with locally advanced PC are not curable multidisciplinary treatment, so it is necessary to optimize patient selection that can balances toxicity, quality of life and disease control.

Many previous random trials considered concurrent radiotherapy with 5-FU have become a frequently employed treatment for locally advanced PC[19] Many investigators are pursuing phase I and II clinic trials of radiotherapy with new chemotherapeutic agents, such as bevacizumab, erlotinib, gefitinib, gemcitabine, capecitabine,oxaliplatin and paclitaxel, because 5-FU-based chemoradiotherapy have the modest survival benefit[20]. But it has not observed marked improvement of survival. The agent S-1 is an oral fluoropyrimidine derivative, which has demonstrated mild toxicity and excellent efficacy in patients with metastatic and locally advanced PC[21-24]. Therefore, it can be recommended as an effective treatment for locally advanced PC because of many clinic trails of concurrent chemoradiotherapy with S-1 for locally advanced PC is considered a well-tolerated, promising regimen[25-29].

However, a lot of patients with locally advanced PC who received upfront chemoradioation were found metastases soon after they completed therapy. Thus, in some clinical trials, induction chemotherapy such as gemcitabine and S-1 followed by chemoradiotherapy as well as this study demonstrated promising activity in treatment of locally advanced PC. It is required that further consideration of radiation schedule and duration of induction chemotherapy to enhance the efficacy of this treatment strategy[30-34].

In this study, combination of S-1 with gemcitabine followed by oral S-1 with concurrent radiotherapy and maintenance with S-1 in the patients who suffer from locally advanced pancreatic cancer was tested. It was easy to administer and had a relative low toxicity that the combination of standard-dose IMRT (50.4 Gy/28 fractions) and full-dose S-1 (80 mg/m2). Moreover, it can improve local control and prevent systemic tumor spread that this regimenmight benefit the patient with locally advanced pancreatic cancer. There was 17 patients (53.1%) with partial response, 9 (28.1%) with stable disease, and4 (12.5%) with progressive disease. Median overall survival and median progression-free survival were 15.2 mo and 9.3 mo, respectively. It was 75% and 34.4% that the survival rates of 1 year and 2 years, respectively. As acute haematological toxicity, grades 4 toxicities were not observed and grade 3 neutropenia was observed in only two patient.As acute nonhaematological toxicity, grade 3 AST elevation (two patient), grade 3 vomiting (four patient), and.grade 3 anorexia and nausea (eight patients) and grade 3 haemorrhagic gastritis (one patient) were observed. We observed duodenal ulcer 7 mo after treatment in one patient as a late toxicity, but no other late toxicity occurred.

Thus, with regard to the antitumor activity of this treatment, S-1 at a daily dose of 80 mg/m2 was considered to be well tolerated and this dose was deemed recommendable.

In conclusion, regiment of combination of S-1 with gemcitabine and followed by oral S-1 with IMRT and maintenance therapy with S-1 in patients having locally advanced pancreatic cancer is considered a well-tolerated, promising regimen, which can be recommended as an effective treatment for locally advanced PC.

**COMMENTS**

***Background***

In the cancer death, unresectable advanced pancreatic cancer is one of the leading causes. So many patients who received upfront chemoradiation have been found immediate metastases after therapy. Furthermore, the patients received initial chemoradiation maybe experience much more toxicities than the patients only received chemotherapy, and because of these toxicities, the subsequent chemotherapy may be interfered. So it is important that the order in which radiation and chemotherapy are given to the patients with locally advanced pancreatic cancer (PC). Therefore need a good alternative approach to start with several cycles of induction chemotherapy and then to restage the patients. The patients without distant metastases on restaging and have a good performance status, may be consolidated by chemoradiation.

***Research frontiers***

This article could be important for the future evolution of the treatment to patients with locally advanced diease.

***Innovations and breakthroughs***

It has demonstrated that S-1 is an excellent efficacy with mild toxicity oral fluoropyrimidine derivative in patients with metastatic and locally advanced PC. Therefore, it was considered a promising, well-tolerated regimen that concurrent radiotherapy with S-1 therapy for locally advanced PC. But it will be found that many patients to have metastases soon after their upfront chemoradiation is completed. So the induction chemotherapy used in the present study, which perform S-1 and gemcitabine followed by chemoradiotherapy, demonstrated promising activity in locally advanced pancreatic cancer. It is required further consideration of duration of induction chemotherapy and radiation schedule to enhance the efficacy of this treatment strategy. It is considered a well-tolerated promising regimen that induction chemotherapy with S-1 and gemcitabine followed by concurrent IMRT with S-1 and maintenance therapy with S-1 in patients with locally advanced PC.

***Applications***

This procedure has been demonstrated as feasible. A larger patient series is needed to confirm the metabolic advantages of the regimen.

***Terminology***

Stereotactic body radiation therapy (SBRT) or intensity modulated radiation therapy (IMRT) are the newer technologies, it can deliver higher doses of radiation to the tumor bed than traditional methods and limit the dose to normal structures (liver, kidneys, and bowel), because of using modulated, multiple beams of radiation that are likely to be more effective and safer than the older radiation techniques. It has demonstrated excellent efficacy in patients with locally advanced.

***Peer review***

Interesting small series of contemporary studies using aggressive induction chemotherapy with S-1 and gemcitabine,then combination therapy with S-1 and IMRT and maintenance S-1 in patients with locally advanced pancreatic cancer.

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|  100 |  |  |  |  |  |  |
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|  |  |  |  |  |  |  |
| **Survival proportion (%)** |  |  |  |  |  |
| 50 |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
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|  |  |  |  |  |  |  |
|  0 |  6 |  12 | 18 |  24 |  30 |  |
|  |  | **Months after treatment** |  |  |
|  |  |  |  |  |

**Figure 1 Progression-free survival and overall survival curves of 32 patients.**

**Table 1 Characteristics of the patients *n* (%)**

|  |  |
| --- | --- |
| **Characteristics** | **Number of patients** |
| Age (yr) |  |
| Range | 50-69 |
| Median | 55 |
| Gender |  |
| Female | 17 (53.12) |
| Male | 15 (46.88) |
| Karnofsky performance status |  |
| 100 | 20 (62.5) |

**Table 2 Toxicity**

|  |  |
| --- | --- |
|  | **Number of patients** |
|  | **Grade 1** | **Grade 2** | **Grade 3**  | **Grade 4** |
| **Leucocytes** | 10 | 6 | 2 | 0 |
| **Neutrophiles** | 5 | 3 | 0 | 0 |
| **Haemoglobin** | 3 | 2 | 0 | 0 |
| **Platelets** | 2 | 1 | 0 | 0 |
| **Anorexia** | 9 | 7 | 5 | 0 |
| **Nausea** | 4 | 7 | 3 | 0 |
| **Vomiting** | 8 | 6 | 4 | 0 |