Comparative Study of Gemcitabine Plus Cisplatin and Gemcitabine Plus Fluorouracil in the Treatment of Advanced Pancreatic Cancer

Yongqian Shu
Lianke Liu
Lingxiang Liu
Puwen Huang
Kaihua Lu
Yongmei Yin

Cancer Biotherapy Center, the First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, China.

OBJECTIVE To compare the efficacy and toxicity of gemcitabine plus cisplatin and gemcitabine plus fluorouracil in the treatment of advanced pancreatic cancer.

METHODS Sixty patients with advanced pancreatic cancer were randomly divided into a GP group (gemcitabine + cisplatin, 30 cases) and a GF group (gemcitabine + fluorouracil, 30 cases). All patients were treated with gemcitabine at a dose of 1,000mg/m^2 (diluted in 100ml saline solution over 30 min) once a week for 3 consecutive weeks. The GP Group was followed by 40mg cisplatin via intravenous drip on days 15,16,17. Group GF was followed by 500mg/m^2 5-Fu (diluted in 5% glucose-saline (GS) 500ml, intravenously, over 6 hr) every day for five subsequent days.

RESULTS In the GP group, eight cases (32.0%) were PR and MR, the median survival time was 8.7 months, the Clinical Beneficial Rate (CBR) was 57.7%, and the CA19-9 decreased by over 50% in 13 cases (48.1%). In the GF group, 11 cases (45.8%) were PR and MR, the survival time was 10.1 months, the CBR was 82.1%, and CA19-9 decreased by over 50% in 15 cases(53.6%). There was a significant difference in the CBR between the two groups ($P<0.05$). The main toxicities in both groups were leucopenia and thrombocytopenia with no significant difference.

CONCLUSIONS The treatment given to either the GP or GF group is a feasible and well-tolerated chemotherapy regimen for treating advanced pancreatic cancer with improved therapeutic efficacy and few side effects. The median survival period is long and the CBR is high, especially with the GF regimen.

KEYWORDS: gemcitabine, cisplatin, fluorouracil, chemotherapy, pancreatic cancer.

Pancreatic cancer is a common malignancy, with 30,300 possible new cases in the United States in the Year 2002 and about 29,700 deaths[1]. Recently the prevalence rate of pancreatic cancer has elevated yearly. This malignant disease has the characteristic of a short course, progressing quickly, high death rate, and no specific symptoms and signs in the early stage. When the patients are diagnosed, most of them have entered into an advanced stage, so the rate of cure is low. Comprehensive regimens may prolong the survival time. From Oct. 1999 to Dec. 2001, 60 patients with advanced pancreatic cancer were enrolled in our study. The patients were randomly divided into two groups: the first, were treated with gemcitabine plus cisplatin(GP group); the second, with gemcitabine combined with the fluorouracil

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Email: COCR@eyou.com Tel(Fax): 0086-022-23522919

(GF group). The clinical efficacy and toxicities in both groups were investigated.

MATERIALS AND METHODS

Patient Selection

All patients with advanced pancreatic cancer were confirmed histologically or cytologically and were selected for study under the following criteria: 18~70 years of age; a Karnofsky performance status(KPS) ≥ 60; a life expectancy of more than 3 months; adequate hematologic function (as indicated by a white-cell count of at least 4,000 per cubic millimeter and a platelet count of at least 100,000 per cubic millimeter), sufficient heart function, hepatic function(as indicated by a bilirubin level that did not exceed 1.5mg per deciliter [25.6 μmol per liter] , and renal function(as indicated by a creatine level that did not exceed 1.5mg per deciliter [132.6μmol per liter]); no previous chemotherapy or radiotherapy. Chemotherapy was given within 3~4 weeks after the operation. All patients were divided into either the GP or GF group at random.

General Data

The GP group included 30 patients, among them 21 were males and 9 females; the ratio of male to female was 2:1. The ages ranged from 28 years to 68 years with a median age of 49 years. The median KPS was 70 (ranging, 60~80). Four patients died of non-related treatment. One was eliminated because of incomplte data. Twenty five patients were evaluated and 26 patients had an improved clinical response. Toxicities were evaluated following each cycle of a total of 71 cycles.

The GF group included 30 patients, among them 23 were males and 7 females; the male to female ratio was 3.3:1. The ages ranged from 31 to 75 years with a median age of 57 years. The median KPS was 70 (ranging 60~80). Two patients died of non-related treatment. Four had no objectively evaluable criteria at the end of the treatment. Twenty-four patients were evaluated and 28 patients got an evaluable clinical benefit response. Toxicities were evaluated following each cycle of a total of 70 cycles. The *U*-test was employed to analyze pathological types and stages between the two groups.

Treatment regimens

GP group: Gemcitabin(Lilly) at a dose of 1,000 mg/m^2 was added to 100ml of normal saline and administered for 30 min(iv) at days 1,8,15. Cisplatin(Qilu) at a dose of 40 mg added in 500ml of normal saline was given on days 15, 16, 17.

GF group: Gemcitabine at a dose of 1000 mg/m^2 was added to 100ml of normal saline and administered on days 1, 8, 15 for 30 min(iv). Fluorouracil(Nantong) at a dose of 500 mg/m^2 diluted in 5% glucose-saline 500ml was given every day for the first five days of every cycle.

About 1,000ml of normal saline and/or 5% dextrose was given each time after the chemotherapy . In order to prevent vomiting, 5-HT$_3$ inhibitor was routinely administrated intravenously before chemotherapy. Routine blood analysis was done once a week after chemotherapy. If the WBC count was <3.0 ×10^9/L, granulocyte-colony stimulating factor (G-CSF) was given until the WBC reached 4.0×10^9/L.

Liver function, kidney function and an electrocardiogram(ECG) were re-examined every month. Every 28 days constituted one cycle and at least two cycles were given for each patient.

The evaluation of the response and toxicities

The responses to treatment were evaluated according to the World Health Organization (WHO 1981) criteria for solid tumors[2]: complete response(CR), partial response(PR), minor response(MR), stable disease(SD), progressive disease(PD). After the patient achieved PR or MR, radiologic examinations were conducted four weeks later. If the response accorded with the PR or MR criteria, then PR or MR was confirmed. The remission interval was calculated from the date of PR or MR to the date of relapse or progress. The survival interval was calculated from the beginning of chemotherapy to the date of death or the date of the last follow-up. The clinical benefit response (CBR) was defined as ≥50% reduction of pain intensity, ≥50% reduction in daily analgesic required, ≥7% body weight gain , and ≥20 point improvement in the KPS. All these goals should be sustained for at least 4 consecutive weeks. A response was defined if at least one of the above criteria were reached, and others were stable. Inefficacy was defined if none of the above criteria were achieved. A stable disease was defined if all the criteria were stable without any change. The toxicities were evaluated using the WHO recommendations for grading of acute and subacute toxicity criteria[3].

Statistical Analysis

Comparisons of objective responses, clinical benefit responses and toxicities were evaluated with the use of the chi-square test or Fisher's exact probability (SPSS software). CA19-9 was compared with the use of the *U*-test.

Table 1. Immediate objective responses of the GP and GF groups in advanced pancreatic cancer

	Patient No.		PR		MR		NC		PD	
Clinical pathological indexes	GP	GF	GP	GF	GP	GF	GP	GF	GP	GF
Pathological types										
Duct cell carcinoma	23	22	2	3	4	7	12	9	5	3
Acinic cell carcinoma	1	2	1	0	0	1	0	0	0	1
adeno-squamous carcinoma	1	0	0	0	1	0	0	0	0	0
Clinical Stage										
III	19	19	2	2	3	7	10	8	4	2
IV	6	5	1	1	2	1	2	1	1	2
CA19-9 level										
Abnormal	23	23	3	3	4	8	11	8	5	4
Normal	2	1	0	0	1	0	1	1	0	0

RESULTS

Clinical responses

The efficacy rate was evaluated at least at the end of two cycles of chemotherapy. Chest radiography and CT scans were taken before evaluation. Overall 146 cycles of chemotherapy were completed with 60 patients. Of the 25 patients in the GP group, 3 cases were PR, 5 MR, 12 NC, and 5 PD. PR plus MR was 32.0%. The median survival time was 8.7 months (range, 4~23months). Of the 24 patients in the GF group, 3 cases were PR, eight MR, 9 NC, and 4 PD. PR plus MR was 45.8% . The median survival time was 10.1 months (range, 5 ~22.5). There was no CR in either group (Table 1).

Comparison of the CA19-9 level in the two groups

The CA19-9 level in the GP and GF groups was compared(Table 2). There was no significant difference between them. The *P* value>0.05.

Table 2. The changes of CA19-9 of the GP and GF groups in advanced pancreatic cancer

		CA 19-9 levels			
Regimen	Cases	Normal	Abnormal	>50%decreasing	Efficacy(%)
GP	30	3	27	13	48.1*
GF	30	2	28	15	53.6

*To compare between GP and GF, $P>0.05$.

Evaluation of the CBR

Of 26 patients in the GP group, a CBR was achieved in 15 (57.7%); While in the GF group, it was 82.1% (Table 3).

Toxicities

Bone marrow toxicity was a main side-effect in the GP group. The incidence rate of leukopenia was 95.8% (68/71), Grade III~IV accounting for 8.5% (6/71). G-CSF (75~150μg per day) at the 56th cycle was given to 36.7%(11/30)of the patients. Decreased hemoglobin was seen in 60.6%(43/71), but Grade III occurred only in two patients. The incidence rate of thrombocytopenia was 88.7% (63/71), and Grade III/IV was 32.4% (23/71). As anti-emetics were given simultaneously, severe nausea/vomiting occurred in only a few patients. Sixteen patients showed different degrees of hepatic dysfunction after 16 cycles, but were not seen above Grade III. At the same time mild kidney impairment was detected after 6 cycles, the main manifestation was the elevation of blood urea nitrogen. Chemotherapy-related death did not occur.

Bone marrow toxicity was also a main side effect in the GP group. The incidence rate of leukopenia was 97.1% (68/70), and Grade III~IV accounted for 7.1% (5/70); reduction of hemoglubin was seen in 64.3% (45/70), and Grade III appeared after 4 cycles. Thrombocytopenia was 92.9% (65/70), and Grade III/IV was 35.7%(25/70). Since platelets were given on a timely basis, severe complications, such as intracranial hemorrhage, were avoided. The 5-HT3 receptor inhibitor ondansetron or granisetron was used for prophylactic treatment, thus reducing severe nausea/vomiting to a few patients. Oral ulcer occurred at 10 cycles, but only one was Grade III. Diarrhea was observed at 13 cycles, and Grade III toxicity appeared at the 3rd cycle . Different hepatic dysfunctions had taken place at 23 cycles, but only one Grade III. The mild kidney dysfunction only occurred in one cycle. Chemotherapy-related death did not occur(Table 4) .

DISCUSSION

Pancreatic cancer is a common malignancy of the digestive system. Over the past decade the incidence rate

Table 3. CBR of the GP and GF groups in the treatment of advanced pancreatic cancer (cases)

Regime	Cases No.	Pain Relief	Sustained median time of pain relief	Reduction inanalgesic consumption	Improvement of KPS	Body weight gain	Effective	Ineffective	Efficacy
GP	26	19	43	10	8	5	15*	11	57.7*
GF	28	22	51	18	11	8	23*	5	82.1

* $P<0.05$

has elevated yearly in the world [4]. About 80% of patients have a veiled onset, with atypical symptoms. When they are diagnosed, most of them are in an advanced stage and are inoperable.In a 1998 report total 1- and 5- year survival rates were under 10% and 1% respectively, and the median survival period was 3~4 months[5]. Pancreatic cancer is insensitive to radiotherapy, and the efficacy of single-agent chemotherapy is below 10%. Comparatively effective drugs were 5-Fu, MMC, EPI, IFO, etc[6].

Gemcitabine is a deoxycytidine analogue, having a chemical name of 2′-deoxy-2′,2′-difluorodeoxycytidine hydrochloride (β-isomer)and abbreviated to difluorocytidine. It is an inhibitor of ribonucleotide reductase. In cells, it is phosphorylated to its active diphosphat(dFdCDP)and triphosphate(dFdCTP) forms by deoxycytidylate kinase. dFdCDP inhibits the ribonucleotide reductase, so the amount of deoxynucleotide, which is necessary for DNA synthesis and repair, decreases. Low dCTP relieves the normal negative feedback on deoxycytidine kinase, which leads to the more accumulation of dFdCTP. At the same time the dFdCTP inhibits the deamination of dFdCMP by deoxycytidine deaminase induced by dCTP, and dFdCTP inhibits deoxycytidine deaminase directly, which causes more dFdCMP to transform to active diphosphate(dFdCDP) and triphosphate(dFdCTP) forms. The dFdCTP can be incorporated into DNA and inhibit DNA synthesis through its competition with dCTP. The dFdCTP is inserted into the sites instead of deoxycytidine in linear DNA, and pairs with guanosines. Then the molecules of gemcitabine are masked by guanosines, which prevents the action of ribonucleic acid exonuclease. So DNA synthesis arrests, further DNA breaks, and the cell dies[7].

The clinical beneficial response of routine combination of leucovorin and 5-Fu was 19%[8]. The efficacy of gemcitabine for advanced pancreatic cancer was confirmed in phase II/III clinical trials. Rothenberg *et al.* [9] demonstrated that single-agent 5-Fu did not change the prognosis of advanced or metastatic pancreatic carcinoma. Clinical symptoms were improved in 27% of the patients, the median survival period was 3.8 months, and the 1-year survival rate was 4%, the median time to progression was 2.5 months, the median time of treatment failure was 2.1 months. Berlin *et al.*[10] reported that, in their phase I clinical trial, gemcitabine combined with 5-Fu plus CF was used to treat 21 patients with pancreatic cancer. Seven patients showed stable disease, and the general conditions of six patients were improved.

Based on the values obtained for the CA 19-9, which decreased ≥20% compared to its baseline, the regimes including gemcitabine were more effective[11]. In our report, the values of CA 19-9 in the GF group (53.6%) decreased more than those of the GP group (48.1%). The median survival time for the GF group was 10.1 months, longer than those of the GP group (8.7 months). It was confirmed that CA 19-9 was an independent survival prognostic factor and its early decrease predicted the susceptibility to chemotherapy.

GF and GP regimens were adopted to treat the advanced pancreatic cancer in our report. The objective effective rate of the GP group was 32.0%(8/25), and that of the GF group was 45.8%(11/24). The CBR of the former regimen was 57.7%(15/26), and the latter was 82.1%(23/28). Two patients with multi-metastasis in abdominal lymph nodes in the GF group were treated by chemotherapy combined with high-intensity focused ultrasound (HIFU) therapy. The pain was significantly relieved, and the positive signs of FDG images were converted to negative.

The main hematological toxicity of gemcitabine was thrombocytopenia. The incidence rate of thrombocytopenia in the GF group (92.9%) was higher than that in the GP group (88.7%), but severe complications, such as intracranial hemorrhage, were not observed in either group. The incidence rates of nausea/vomiting and kidney function failure in the GP group were higher than those in the GF group, but the incidence rates of oral ulcer, diarrhea, cytopenia and liver dysfunction were higher in the GF group.

The objective effective rate of gemcitabine combined with 5-Fu or cisplatin was higher than that of a conventional chemotherapy regimen, moreover the CBR was also increased and the toxicities were tolerable. This study also indicated that the CBR of the GF

Table 4. Comparison of toxicities of the GP/GF groups in advanced pancreatic cancers (GP/GF)

	Different degrees of toxicities(cycles)						
Toxicities	0	I	II	III	IV	III–IV	Incidence rate
Leukopenia	3/2	37/41	25/22	4/4	2/1	8.5/7.1	95.8/97.1
Thrombocytopenia	8/5	21/24	19/16	18/21	5/4	32.4/35.7	88.7/92.9
Reduction of Hb	28/25	17/16	24/25	2/4	0/0	2.8/5.7	60.6/64.3
Elevation of transaminase	55/47	14/19	2/3	0/1	0/0	0/1.4	22.5/32.9
Elevation of creatinine/urea nitrogen	65/59	4/1	2/0	0/0	0/0	0/0	8.5/1.4
Nausea/vomiting	49/58	18/10	3/1	1/0	0/1	1.4/1.4	31.0/17.1
Oral ulcer	69/60	1/6	1/3	0/1	0/0	0/1.4	2.8/14.3
Diarrhea	67/57	3/8	0/3	0/3	0/0	0/4.3	5.6/18.6

Note: Comparison of Grade III or above toxicities of GP and GF, all $P > 0.05$.

regimen was higher than that of the GP regimen .Because only few patients were studied, further investigation is needed. Our study also confirmed the possibility of CA 19–9 dynamic alteration as an early predictable marker of chemosensitivity. The clinical efficacy, especially the CBR, may be further improved when GF–type therapy, combined with HIFU,is used to treat advanced pancreatic cancer. This is worthy of further investigation.

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