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ORIGINAL ARTICLE

Irinotecan monotherapy as second-line treatment in advanced pancreatic cancer

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Abstract
Purpose The phase II study was conducted to evaluate the efficacy and safety of irinotecan as salvage single-agent chemotherapy in patients with advanced pancreatic cancer.
Methods Patients with measurable metastatic pancreatic cancer, progressive after previous gemcitabine-based chemotherapy were treated with irinotecan 150 mg/m^2 every 2 weeks. Treatment was repeated until disease progression or unacceptable toxicity.
Results Between March 2004 to February 2007, 33 patients were registered and treated with irinotecan monotherapy. The patients' median age was 59 years (range 36–70) and two had an ECOG performance status of 2. A total of 167 chemotherapy cycles were delivered (median, 4; range 2–12). In an intent-to-treat analysis, three (9%) confirmed partial response and 13 patients with stable disease were observed for a disease control rate of 48%. The median progression-free and overall survivals were 2.0 months (95% CI, 0.7–3.3) and 6.6 months (95% CI, 5.8–7.4), respectively. Toxic effects were mainly gastrointestinal (nausea in 64% of patients, diarrhea in 36%), Toxicity profiles were generally predictable and manageable, and there was no treatment-related death.
Conclusions Second-line chemotherapy with single-agent irinotecan is marginally effective and well tolerated regimen for gemcitabine-pretreated patients with advanced pancreatic cancer.

Keywords Pancreatic cancer · Irinotecan · Second line chemotherapy · Gemcitabine failure

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Introduction

Pancreatic adenocarcinoma is the fifth leading cause of cancer related death in Korea, and its incidence has been constantly rising in recent years [1]. The highest cure rate occurs if the tumor is truly localized to the pancreas; however, this stage of disease accounts for fewer than 20% of cases [10]. For patients with unresectable, locally advanced, or metastatic disease, single-agent gemcitabine provides clinical benefit and a survival advantage over treatment with bolus 5-fluorouracil (5-FU) and is considered to be the current standard of care for this population [4]. However, over 90% of patients with advanced pancreatic cancer who received gemcitabine-based chemotherapy failed to achieve response and even in these responders, the duration of responses was as short as a few months [7]. Furthermore, the treatment of advanced pancreatic cancer patients after failure with first-line chemotherapy remains controversial. Due to poor performance status and rapid clinical deterioration, approximately half of advanced pancreatic cancer patients who progress following gemcitabine-based chemotherapy are not eligible for second-line chemotherapy. Therefore, only a limited number of studies have investigated the role of second-line chemotherapy in advanced pancreatic cancer.

Irinotecan (CPT-11; Campto®) is a semisynthetic, water-soluble derivative of the plant alkaloid camptothecin. Following conversion to its active metabolite, SN-38, irinotecan acts by inhibiting DNA topoisomerase I, thereby interfering with DNA replication and cell division [5]. Results of irinotecan-containing regimen in the treatment of gastrointestinal cancers are encouraging [6, 13]. Irinotecan is also highly active on pancreatic tumor cells in culture and in xenograft models [2]. Irinotecan monotherapy has been tested in patients with previously untreated advanced pancreatic cancer [19], and the activity observed with irinotecan appears to be at least equivalent, if not better, than gemcitabine or 5-FU [11]. Based on these data we initiated a phase II study of single-agent irinotecan as second-line chemotherapy in patients with advanced pancreatic cancer, previously treated with gemcitabine-based chemotherapy.

Patients and methods

Patients aged 75 years or less with histologically-confirmed advanced pancreatic cancer, progressive after one prior gemcitabine-based chemotherapy for advanced disease, were enrolled for this single-center phase II study. Other eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, the presence of at least one measurable lesions outside the primary tumor, adequate bone marrow (neutrophil count > 1,500/mm^3, platelet count > 100,000/mm^3), hepatic (AST/ALT $\leq 2.5\times$ upper limits of normal; bilirubin ≤ 1.5 mg/dl) and renal (creatinine clearance ≥ 60 ml/min or creatinine $\leq$ upper limits of normal) functions. Adjuvant chemotherapy and/or radiotherapy that had been completed more than 6 months before registration were allowed. In addition, at least 4 weeks had to have elapsed since the last chemotherapy administration. Patients with uncontrolled leptomeningeal or brain metastases, a second malignancy other than non-melanoma skin carcinoma or carcinoma in situ of the cervix, extensive radiotherapy within the previous 4 weeks, uncontrolled comorbid illness and/or active infections were ineligible. All patients provided a signed informed consent in accordance with our institutional review board guidelines.

Treatment

Irinotecan was administered as intravenous infusion over 90 min at a starting dose of 150 mg/m^2. Each cycle was repeated every 2 weeks until disease progression or unacceptable toxicity was noted, or the patients refused further treatment. The prophylactic use of hematopoietic growth factors was not allowed during treatment, except for patients with febrile neutropenia or grade 4 myelosuppression at the investigators' discretion. No primary prophylaxis with atropine was given unless a patient experienced grade ≥ 2 diarrhea. Supportive care, including administration of blood transfusions, antiemetics and analgesics was provided according to the department policy. Follow-up history, physical examinations and toxicity assessments were performed before each 2-week cycle of therapy. The dosage of the subsequent cycles was adjusted according to the toxic effects that developed during the preceding cycle. Chemotherapy was delayed for a week if neutrophil count was <1,500/mm^3 or the platelet count was <100,000/mm^3 on day 1. If nadir neutrophil count was <500/mm^3 or the nadir platelet count was <50,000/mm^3 then the doses of irinotecan was reduced to 80% of the initial doses. If grade ≥ 2 non-hematologic toxicity occurred, chemotherapy was withheld until recovery to grade ≤ 1. In case of grade ≥ 2 diarrhea, patients were treated with loperamide (starting dose 4 mg, followed by 2 mg every 2 h as long as diarrhea continued, to a maximum dose of 16 mg/day). The patients were hospitalized and treated with antibiotics when the diarrhea persisted for more than 24 h or it occurred in combination with neutropenia, fever or dehydration. If chemotherapy was delayed > 2 weeks, then the patient was treated off the protocol. Dose re-escalation was not permitted.

Evaluation

The baseline evaluation included a complete medical history and physical examinations, blood counts, serum chemistry, CA19-9 levels, chest X-ray, and abdominopelvic computed tomography (CT) scan. Follow-up history, physical examinations and toxicity assessment were performed before each 2-week cycle of treatment. Toxicity grading was based on the National Cancer Institute criteria (NCI-CTCAE version 3). The first evaluation with imaging was done after the completion of four cycles of chemotherapy. Tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumours (RECIST) [16] and was assessed by abdominopelvic CT scan and by the same tests used initially to stage the tumor. Responses were confirmed at least 4 weeks later and reviewed by independent investigator later at the time of analyses. Progression in the non-measurable lesions that led to deterioration of the patient's status was classified as progressive disease, regardless of the status of the measurable lesions. Patients were evaluated for response if they received ≥ 1 cycles of treatment.

Statistical considerations

The primary objective of this study was to determine if the disease control rate (objective response plus stable disease) of irinotecan monotherapy could exceed 40%. According to

the Fleming's single-stage method [8], 33 eligible patients were required to detect a difference in response rate between 20 and 40% with 80% power and $P < 0.05$. The starting point of various time intervals was the first day of second-line chemotherapy. The date of disease progression or death from causes other than advanced pancreatic cancer was used in calculating progression-free survival. Time to death, whatever the cause, was used to calculate overall survival. Survival was calculated by the Kaplan–Meier method. All analyses were performed on the intent-to-treat population, defined as all the registered patients who signed an informed consent.

Results

Between March 2004 and February 2007, 33 eligible patients entered the study (Table 1). The median age was 59 years (range 36–70) with a male preponderance. All patients but two had an ECOG performance status of 0 or 1. Fourteen (42%) patients had recurrent disease after curative surgery. Most common sites of metastatic disease were liver (21 patients) and intra-abdominal lymph nodes (15 patients). All patients were previously treated with gemcitabine-based chemotherapy, either as monotherapy (10 patients) or in combination with cisplatin and/or fluoropyrimidines. Fourteen (42%) patients experienced an objective response to these first-line treatments.

Safety

A total of 167 chemotherapy cycles were delivered with a median of 4 per patient (range 2–12). Of the 33 patients who started irinotecan monotherapy, the main reasons for discontinuing treatment were progressive disease (70%) and toxicity (30%). Dose reduction was required in three patients. All eligible patients were evaluable for toxic effects (Table 2). The most frequently encountered toxic effects were gastrointestinal toxicities including nausea and diarrhea, which were managed with rest, dose reduction, or treatment discontinuation. Even if all patients were pretreated with cytotoxic chemotherapy, grade ≥ 3 neutropenia was occurred in only two patients. No patient died of toxicity during treatment. The median dose intensity of irinotecan 68 mg/m^2 week^{-1} corresponded to 91% of the scheduled dose.

Efficacy

We obtained three partial responses (overall response rate, 9%; 95% confidence interval [CI], 0–18%), plus 13 stable diseases. Disease control (objective response plus stable disease) was achieved in 16 (48%) patients treated with irinotecan monotherapy. Two patients who had an ECOG performance status of 2 did not respond to the second-line regimen of this study. All three patients who achieved a partial response had a corresponding decrease in serum CA19-9 level by more than 50% as compared with the baseline value. Of 30 evaluable patients, 10 (33%) showed more than 50% decrease in serum CA19-9 level from their baseline value. Although not specified in the protocol, we offered further third-line chemotherapy to 12 patients (36%) after failure.

Table 1 Patient characteristics (total $N = 33$)

	No. of patients	%
Age, years		
Median (Range)	59 (36–77)	
Male gender	24	73
ECOG performance status		
0	6	18
1	25	76
2	2	6
Metastatic site(s)[a]		
Liver	21	64
Abdominal lymph nodes	15	45
Lung and/or malignant pleural effusion	3	9
Peritoneum	3	9
Prior therapy for curative intent		
Surgery	14	42
Adjuvant therapy	10	30
First-line chemotherapy for advanced disease		
Gemcitabine monotherapy	10	30
Gemcitabine + fluoropyrimidines	15	46
Gemcitabine + cisplatin	5	15
Gemcitabine + fluoropyrimidines + cisplatin	3	9

ECOG the Eastern Cooperative Oncology Group

[a] Because patients could have metastases at multiple sites, the total numbers of metastases are greater than the number of patients

Table 2 Maximum grade toxicity per patient (total $N = 33$)

	Grade 1–2		Grade 3–4	
	N	%	*N*	%
Anemia	12	36	0	0
Neutropenia	9	27	2	6
Thrombocytopenia	4	12	0	0
Nausea and vomiting	18	55	3	9
Anorexia	17	52	3	9
Stomatitis	2	6	0	0
Diarrhea	11	33	1	3
Fatigue	10	30	0	0

The median progression-free survival was 2.0 months (95% CI, 0.7–3.3 months), and the overall survival time was 6.6 months (95% CI, 5.8–7.4 months), as shown in Fig. 1. At the time of present analyses, 32 patients (97%) died.

Discussion

Advanced pancreatic cancer is an incurable condition where the aim of treatment is to improve survival and to palliate symptoms. Gemcitabine is used widely as the standard first line chemotherapy for patients with advanced pancreatic cancer [4]. However, when patients develop disease progression eventually, or more frequently, do not response to gemcitabine, no established second-line therapy can be offered. There is no evidence that second-line chemotherapy in patients with advanced pancreatic cancer will result in substantial prolongation of survival and there is potential for toxicity from the treatment. Despite favorable outcomes seen in some phase II trials of second-line chemotherapy for advanced pancreatic cancer [9], the results from phase II trials may not be generalized to the routine clinical situation. Eligibility criteria tend to result in the recruitment of a relatively good prognostic group.

Second-line chemotherapy is classically considered ineffective against advanced pancreatic cancer. In large randomized studies performed in patients with advanced pancreatic cancer, 16–57% of patients received salvage chemotherapy after failure [3]. More than half of the patients may not receive second-line chemotherapy due to rapid clinical deterioration. However, patients and physicians have difficulty with accepting only supportive care without the possibility of systemic anticancer effects. The availability of a number of new drugs with a favorable toxicity profile, as well as their non-overlapping mechanisms of action, has provided opportunities to re-evaluate the role of second-line treatment in patients with advanced pancreatic cancer. Increasing number of patients who have a refractory advanced pancreatic cancer are still in a good performance status when progression on gemcitabine-based chemotherapy is detected. Therefore, there is a need for effective drugs as salvage treatment after gemcitabine failure, especially for selected patient population with preserved performance status.

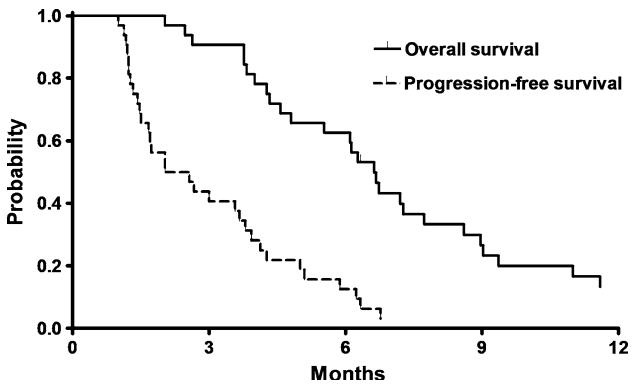

Fig. 1 Kaplan–Meier estimates of progression-free survival and overall survival

This phase II study was on a relatively small group of patients, but it is distinctive in the target patient population. We investigated the activity and tolerability of single-agent irinotecan in patients with advanced pancreatic cancer failing gemcitabine-based first-line chemotherapy. Using this biweekly schedule of irinotecan, we obtained an impressive progression-free and overall survival of 2.0 and 6.6 months, respectively. Toxicity profiles in our study were generally mild, and severe hematologic toxicities were infrequent. This favorable toxicity profile of the regimen is of importance, since the primary objective of second-line treatment in advanced pancreatic cancer patients is palliative in nature. Moreover, the relative dose intensity of irinotecan was 91%. This satisfactory dose intensity, together with relatively good performance status of patients, may in part account for the favorable outcomes in this pretreated patient population. Considering that a significant number of patients had an objective response to the first-line chemotherapy, it is likely that the results represent a possible selection of patients with a relatively good prognosis.

Irinotecan-based chemotherapy regimens have been tested in patients with advanced pancreatic cancer. In the first-line setting, phase III studies of irinotecan and gemcitabine combination chemotherapy showed no survival benefit over gemcitabine monotherapy [12, 14]. Second-line irinotecan has shown some degree of activity as monotherapy [11], or in combination with other agents [15, 18]. In general, second-line treatment in advanced pancreatic cancer should be used to prolong survival and improve the quality of life of the patients. These goals should be met through the use of well tolerated regimens with a reasonably convenient administration scheme in order to avoid frequent visit to the clinic. Because many advanced pancreatic cancer patients have poor performance status and a short life expectancy, it seems more prudent to avoid multidrug combination chemotherapy in salvage regimen for reasons of safety. Single-agent irinotecan has been tested in first-line setting of advanced pancreatic cancer [17], and an encouraging median overall survival of 7.3 months was reported.

Although the results presented here are from a relatively small phase II study, the data suggest that the use of irinotecan monotherapy for advanced pancreatic cancer patients failing after prior gemcitabine is effective and feasible. On the other hand, patients with poor performance status (i.e., ECOG 2) did not respond to second-line therapy. The

disappointing findings in these patients indicate that second-line chemotherapy in patients with poor performance status should be given in caution and consideration should be warranted to exclude such patients from future clinical trials. We hope that this study could result in a prospective study to determine whether this activity translates into actual improvement in survival and quality of life in patients with pretreated advanced pancreatic cancer. Given our data and pending the results of larger randomized studies [3], a reasonable practice at this point would be to offer a chance of salvage chemotherapy to advanced pancreatic cancer patients who failed gemcitabine-based chemotherapy, if they preserve a good performance status.

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