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ORIGINAL ARTICLE

A phase II trial of gemcitabine plus capecitabine for patients with advanced pancreatic adenocarcinoma

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Abstract
Purpose While gemcitabine (GEM) is widely accepted for the treatment of advanced pancreatic cancer, capecitabine (CAP) has shown single agent activity and promising efficacy in combination with GEM. This phase II study was conducted to evaluate the efficacy and toxicity of GEM combined with dose escalated 14-day CAP as first-line chemotherapy for advanced pancreatic cancer. In addition, we also analyzed the correlation between CA19-9 response and clinical outcomes.
Methods Patients had advanced pancreatic adenocarcinoma, no prior systemic chemotherapy other than that given concurrently with radiation therapy, at lease one measurable disease, and adequate organ functions. The patients were treated with GEM 1,000 mg/m^2 IV on days 1, 8 and CAP 1,000 mg/m^2 twice a day PO on days 1–14, in 21-day cycles.
Results The objective RR among 45 patients was 40.0% (95% CI; 25.1–54.9), including 1CR (2.2%). The median TTP and OS were 5.4 months (95% CI; 1.8–9.0) and 10.4 months (95% CI; 6.2–14.5), respectively. Patients with ≥25% decline of serum CA19-9 had significantly better outcomes in terms of TTP and OS than those who did not ($P < 0.03$). The most frequent, grade 3–4, non-hematologic toxicity was hand–foot syndrome (6.7%).
Conclusions The combination of GEM with dose escalated 14-day CAP is well tolerated and offers encouraging activity in the treatment of advanced pancreatic cancer. In addition, CA19-9 response correlates well with clinical outcomes in this population.

Keywords Gemcitabine · Capecitabine · Pancreatic cancer · CA19-9

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Introduction

Until 1997, fluorouracil (5-FU) was the most widely used drug for advanced pancreatic cancer, with an objective response rate of 0–7% [1, 2]. The greatest change in the treatment of advanced pancreatic cancer has been acceptance of gemcitabine (GEM) monotherapy as a standard first-line treatment on the basis of the results of a randomized trial comparing GEM with bolus 5-FU [2]. GEM was superior to 5-FU in terms of median survival, 1-year survival, and clinical response in this pivotal phase III trial. However, the overall objective response rate still remains low. Since then, the strategy to improve the treatment of advanced and metastatic pancreatic cancer has focused on adding a second agent to GEM and it has been safely

combined with several other cytotoxic agents. However, this strategy has not been overly successful [3–6]. Most patients with advanced pancreatic cancer usually have poor performance status due to rapidly progressive tumor kinetics. Therefore, a relatively few number of patients could be candidates for palliative chemotherapy with cytotoxic agents.

Capecitabine (CAP) is an oral precursor of 5-FU. As conversion of CAP to 5-FU is dependent on an enzyme (thymidine phosphorylase), preferentially expressed in malignant cells, it is thought to exert its main effect, locally, within the tumor [7]. Phase II clinical data provided evidence for the activity of CAP in advanced pancreatic cancer [8]. The combination of GEM and CAP seems attractive since the drugs have different mechanisms of action and non-overlapping toxicities. Furthermore, the combination is convenient since CAP can be orally administered with similar effectiveness as intravenously infused 5-FU [9, 10]. It has been considered one of the agents that is most safely combined with GEM in terms of toxicities and would be expected to achieve improved clinical benefits in patients with advanced pancreatic cancer and good performance status. In a recent interim analysis of phase III study comparing the GEM–CAP combination to GEM alone [11], which consisted of GEM 1,000 mg/m^2 on days 1, 8 and CAP 650 mg/m^2 twice a day on days 1–14 every 3 weeks, the outcomes of GEM–CAP were not significantly better than for patients who received GEM alone. Given this, we conducted a phase II trial to evaluate the efficacy and toxicity of GEM combined with dose escalated 14-day CAP as first line chemotherapy in this population.

Carbohydrate antigen 19-9 (CA19-9) is an effective, non-invasive diagnostic or prognostic tool for pancreatic cancer [12–14]. In a recent study, serial CA19-9 measurements correlated well with clinical outcomes in patients receiving fixed-dose GEM for advanced pancreatic cancer and this suggested that decline in this biomarker should be entertained for possible use as a surrogate end point in clinical trials for the selection of new treatments [15]. In this context, we also investigated whether CA19-9 decline served as a prognostic factor for survival and time to tumor progression.

Patients and methods

Patient selection

Eligible patients had histologically or cytologically confirmed adenocarcinoma of the pancreas and unresectable, locally advanced or metastatic disease with at least one measurable lesion. Performance status was Eastern Cooperative Oncology Group (ECOG) 0–1. None of them had undergone either previous palliative chemotherapy or radiotherapy, except for postoperative adjuvant therapy. Adequate bone marrow reserves, normal renal and liver function tests were required. Patients with active infection, malnutrition or a second primary tumor were excluded from the study. Written informed consent was required from all patients before the start of treatment.

Treatment

GEM was given as an intravenous infusion for 30 min on days 1 and 8 of each cycle at a dose of 1,000 mg/m^2. CAP was administered, orally, at a dose of 1,000 mg/m^2 twice a day for 14 consecutive days followed by 1 week of rest. Cycles were repeated every 21 days, provided that patients had recovered drug-related side effects to grade 1 or less. Treatment was administered up to six cycles or until disease progression occurred. However, treatment was continued up to nine cycles in patients who achieved partial response or stable disease with clinical benefits at the physicians' discretion. In cases of febrile neutropenia or grade 3 or 4 neutropenia, GEM and CAP doses were reduced by 20%. The dose of CAP was reduced by 20% in cases of grade 3 or 4 mucositis, diarrhea, or hand-foot syndrome. Chemotherapy was discontinued if these toxicities persisted for two consecutive weeks. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.

Assessments

Pretreatment evaluation included the patient's history, physical examination, performance status, standard chest X-ray, complete blood count, blood chemistry, serum CA19-9, and CT scan of the pancreas including lower lung, abdomen and pelvis. Additional imaging studies were performed as clinically indicated. Complete blood count with differential was performed on days 1 and 8, and a detailed medical and physical examination was completed before each course of treatment, in order to document symptoms of the disease and treatment toxicities. During treatment, biochemical tests, serum CA 19-9 level, and chest X-rays were performed every 3 weeks. Lesions were measured by CT scans, which were performed every two chemotherapy cycles. Other laboratory tests or imaging studies for identifying local or distant recurrences were performed depending on subjective symptoms and signs. Objective response to the treatment was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), and objective response rate was defined as the sum of complete (CR) and partial response rates (PR).

Pain improvement was defined as >50% decreased analgesic consumption with subjective decreased pain intensity.

We used "numeric rating scale (NRS)" to assess the subjective pain intensity. Weight gain was defined as an increase of >10% of pretreatment body weight, which was sustained in the next cycle.

Statistical analysis

Sample size was calculated to reject a 20% response rate in favor of a target response rate of 40%, with a significance level of 0.05 and a power of 80%, using Simon's optimal two-stage design. In the initial stage, 13 evaluable patients were to be entered and evaluated for response. If there were less than three responses, accrual was to be terminated. If more than four responses were observed in the first stage, then 30 additional patients were to be entered in the second stage to achieve a target sample size of 43 evaluable patients. Further assessment of the regimen was felt to be warranted if more than 13 responses were observed in the 29 patients.

The overall survival (OS) duration was calculated from the first day of chemotherapy until the date of death or the last documented follow-up. Time to tumor progression (TTP) duration was calculated from the start of chemotherapy until the date of the first documented progression or the last follow-up. Kaplan–Meier survival curves were generated, and the statistical significance of the difference was assessed using the log-rank test. Differences between groups were compared using the Pearson Chi square test.

Results

Patient characteristics

Between September 2002 and November 2005, 45 patients at Samsung Medical Center, Seoul, Korea were enrolled into the trial. Clinical characteristics of enrolled patients are summarized in Table 1. The median age was 55 years (range 33–76) with a male preponderance. All patients had good performance status, corresponding to an ECOG of 0–1. The majority of patients had a moderate or poorly differentiated adenocarcinoma (71.2%). At enrollment, 35 (77.8%) patients had metastatic disease, 10 (22.2%) patients were at the locally advanced stage. The median number of chemotherapy cycles was four (range 1–9).

Table 1 Patient characteristics ($N = 45$)

Age	Range	33–76	
	Median	55	
Sex	Male	33	(73.3%)
	Female	12	(26.7%)
ECOG PS	0	3	(6.7%)
	1	42	(93.3%)
Differentiation	Well differentiated	3	(6.7%)
	Moderately differentiated	16	(35.6%)
	Poorly differentiated	16	(35.6%)
	Undifferentiated	2	(4.4%)
	Unclassified	8	(17.8%)
Primary lesion	Head of pancreas	21	(46.7%)
	Body of pancreas	14	(31.1%)
	Tail of pancreas	8	(17.8%)
	Combined	2	(4.4%)
Stage	Locally advanced disease	10	(22.2%)
	Metastatic disease	35	(77.8%)
Metastatic site	Liver	24	(80.0%)
	Peritoneum	5	(16.7%)
	Lung	3	(10.0%)
	Liver, Lung	2	(6.7%)
	Adrenal	1	(3.3%)
Number of chemotherapy cycles	#1	4	(8.9%)
	#2	10	(22.2%)
	#3	6	(13.3%)
	#4	9	(20.0%)
	#5	4	(8.9%)
	#6	5	(11.1%)
	#7	2	(4.4%)
	#8	2	(4.4%)
	#9	3	(6.7%)

Table 2 Grade 3–4 toxicities ($N = 45$)

Hematologic toxicity		
Anemia	5	(11.1%)
Neutropenia	2	(4.4%)
Febrile neutropenia	1[a]	(2.2%)
Non-hematologic toxicities		
Hand-foot syndrome	3	(6.7%)
Mucositis	1	(2.2%)

[a] Treatment-related mortality

Toxicities

Grade 3–4 toxicities of treatment are shown in Table 2. The most common grade 3–4 side effects were anemia (11.1%), in hematologic toxicity, and hand–foot syndrome (6.7%), in non-hematologic toxicity.

One of the 45 patients (2.2%) died from neutropenic sepsis during treatment. Two patients were treated with a 20% reduced dosage of GEM and CAP due to neutropenia. Two

patients were treated with 20% reduced dosage of CAP due to hand–foot syndrome. One patient discontinued CAP due to severe hand–foot syndrome and mucositis.

Response and survival

More than half of the patients received GEM–CAP chemotherapy for at least four cycles. Responses were analyzed on an intent-to-treat basis. Objective response was observed in 18 of 45 patients (40.0%, 95% CI; 25.1–54.9) including 1 CR (2.2%) and 17 PRs (37.8%). These results are shown in Table 3. Ten of 45 patients (22.2%) showed stable disease (SD) and 17 of 45 patients (37.8%) developed progressive disease (PD). There was no significant difference in response rate due to sex, PS, tumor stage, tumor site, or pathological differentiation. Clinical benefits in terms of pain improvement and weight gain were achieved in 20 of 45 patients (44.4%) and 10 of 45 patients (22.2%), respectively.

During the median follow-up of 12.5 months (95% CI; 10.3–14.7), PD occurred in 33 of 45 patients (73.3%) with a median response duration of 4.3 months (range 1.2–12.3) and 23 of 45 (51.1%) patients died. The median TTP was 5.4 months (95% CI; 1.8–9.0) and the median OS was 10.4 months (95% CI; 6.2–14.5,) (Fig. 1). One-year survival rate was 39.3% (95% CI; 20.7–57.9). Median TTP of locally advanced disease was superior to that of metastatic disease (9.8 months, 95% CI; 7.2–12.4 vs. 4.3 months, 95% CI; 2.2–6.4, $P = 0.05$). However, overall median survival for locally advanced disease was 13.9 months (95% CI 13.9–13.9) and for metastatic disease it was 9.6 months (95% CI 4.6–14.6, $P = 0.19$). There was no survival difference between stages.

Table 3 Objective response rate ($N = 45$)

Complete remission	1	(2.2%)
Partial remission	17	(37.8%)
Stable disease	10	(22.2%)
Progressive disease	17	(37.8%)

Serum CA19-9 and survival

Increased pretreatment serum CA 19-9 levels were observed in 31 of 45 patients (68.9%). Table 4 shows the decline in CA 19-9 ratio to baseline CA19-9 level after two cycles of chemotherapy. In 27 of 45 patients (60.0%), CA 19-9 level was decreased by more than 25% from baseline. Thirteen patients (28.9%) showed either a decline of less than 25% of CA 19-9 level or increased CA 19-9 level after two cycles of chemotherapy.

Patients with a decrease in CA 19-9 level of >25% from baseline after two cycles of chemotherapy had a significantly better median TTP (8.2 months vs. 2.6 months; $P = 0.03$) and median OS (13.9 months vs. 6.0 months; $P = 0.001$) than patients with either a rise or a decline <25% (Fig. 2).

Discussion

Hess et al. [16] reported a phase I/II clinical trial of the GEM–CAP combination. The authors indicated that the doses recommended for phase II studies were GEM 1,000 mg/m^2 given on days 1 and 8, and CAP 650 mg/m^2 twice a day for 14 consecutive days of a 21-day cycle. In 27 patients with measurable disease, they observed one CR and four PRs for an overall response rate of 18.5%. These doses and schedules of GEM–CAP chemotherapy were employed in another phase II study, in Greece, which was a intergroup, multicenter study for the first-line treatment of

Table 4 CA19-9 decline ratio after two cycles of chemotherapy ($N = 45$)

>70%	7	(15.6%)
50–70%	8	(17.8%)
25–50%	12	(26.7%)
<25%	13	(28.9%)
No evaluation	5	(11.1%)

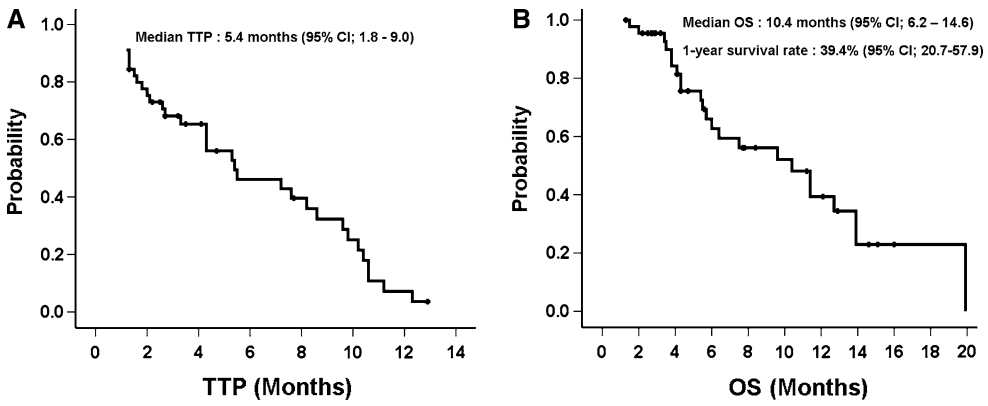

Fig. 1 Time to tumor progression (**a**) and overall survival (**b**)

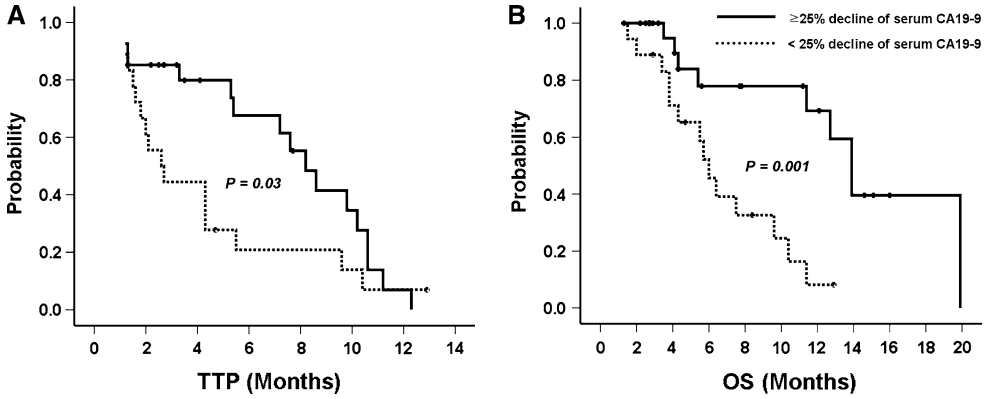

Fig. 2 Time to tumor progression (**a**) and overall survival (**b**) according to decline in the ratio of serum CA19-9

inoperable or metastatic pancreatic cancer with GEM–CAP [17]. In this Hellenic group study, 10 of 53 patients (18.9%) achieved objective responses. The median response time was 3 months (range 1.5–7.0) and the median TTP was 6.5 months (range 3.5–15.5). Median OS was 8 months (range 1.0–15.5) and 1-year survival rate was 34.8%. However, these results were not satisfactory for accepting GEM–CAP as the new standard therapy because the improvement of objective response and survival outcomes were still disappointing. Recently, two randomized phase III studies comparing the GEM–CAP combination to GEM alone were reported. However, the outcomes were conflicting. Hermann et al. [11] reported an OS of 8.4 months and progression-free survival (PFS) of 4.8 months for patients who received combination treatment, which consisted of GEM 1,000 mg/m^2 on days 1, 8 and CAP 650 mg/m^2 twice a day on days 1–14 every 3 weeks. These results were not significantly better, statistically, than for patients who received GEM alone (7.3 months, $p = 0.314$, and 4.0 months, $p = 0.207$, respectively). In another UK NCRI study [18], a higher dose of CAP with standard does of GEM (GEM 1,000 mg/m^2 IV weekly for three times, CAP 1,660 mg/m^2/day po for 21 days every 4 weeks) was used in a combination schedule. A statistically significant improvement in OS (7.4 months vs. 6.0 months; HR 0.80, 95%CI 0.65–0.98; $P = 0.026$) and 1-year survival (26% vs. 19%) were observed in this interim analysis. Grade 3–4 toxicity was similar between arms except for more neutropenia (17% vs. 11%) in the combination arm. Although, these trials may have predictable results, it remains unclear which dosage of CAP, added to GEM, would produce more favorable outcomes than that of GEM monotherapy. Therefore, we proceeded with the present study with a dose escalation of CAP to 1,000 mg/m^2 twice a day. Compared with these previous trials, a more than twofold increase in objective response rate (40.0%), with similar toxicity profiles, was observed. It stemmed from the effect on relatively high percentage of patients with excellent PS and young median ages in our study. However, this response rate should be interpreted with caution because there was no independent radiological verification in this study. It is well known that extensive desmoplasia and surrounding inflammation in pancreatic cancer make it difficult to measure tumor responses accurately using conventional methods. In addition, despite of high response rate, it is not encouraging for TTP (5.4 months) and OS (10.4 months) in the present study compared with previous GEM–CAP studies.

The toxicity of the GEM–CAP combination in present study was well tolerated and mainly associated with anemia (11.1%) and hand–foot syndrome (6.7%) in grade 3–4 toxicity. Comparing the toxicity profile with previous GEM–CAP studies, minor differences were found. Hess et al. [16] observed no hand–foot syndrome in their phase I/II study, and grade 3 toxicity occurring in less than 5% of the patients and only one patient developed hand–foot syndrome (grade 2) in the Hellenic group study [17]. Compared to the toxicity profile of both previous phase III studies [11, 18], the low incidence of skin toxicity observed in phase III studies may be attributed to the lower daily dose of CAP.

In a recent randomized phase III trial of GEM plus erlotinib compared to GEM alone in patients with advanced pancreatic cancer [19], the addition of erlotinib to GEM significantly improves OS and PFS in advanced pancreatic cancer. However, this study showed only 9% of overall response rate, 3.8 months of median progression-free survival and 6.4 months of median OS, it seems to be relatively inferior outcomes to our results. Although, there is no comparative trial of GEM–CAP versus GEM plus erlotinib, CAP would be more effective oral agent than erlotinib as a combination with GEM.

In the present study, the combination of GEM–CAP also had a significant effect on serum CA 19-9 level. CA 19-9 level was decreased, after two cycles of chemotherapy, by >25% in 27 patients (60.0%) and >50% in 15 patients (33.3%). Patients with >25% decline of serum CA 19-9 had significantly better outcomes in terms of TTP and OS than those who did not (Fig. 2). A decrease in the tumor marker CA 19-9 can identify patients who benefit from this treatment and can be used as a prognostic marker for survival.

Similarly, previous studies also reported that patients with a >20 or 25% drop in CA 19-9 levels, during treatment with GEM in advanced pancreatic cancer, had significantly longer median survival than patients with a rise or a decrease of <20 or 25% [15, 20, 21].

In conclusion, GEM–CAP combination chemotherapy with a higher dose of CAP for 14 days, as first-line treatment in patients of advanced pancreatic cancer with good performance status, is an effective and convenient regimen with a high objective response rate and an acceptable toxicity profile. In addition, a decrease of serum CA19-9 level from baseline, during treatment, was an independent prognostic factor for survival. In spite of the high response rate, unfortunately, this result is not encouraging for TTP and OS. However, different CAP schedules and pharmacogenomics of tolerability in different populations should be evaluated.

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