Cancer Chemother Pharmacol (2008) 62:763–768
DOI 10.1007/s00280-007-0661-y

ORIGINAL ARTICLE

A phase II study of capecitabine plus gemcitabine in patients with locally advanced or metastatic pancreatic cancer

Hong Suk Song · Young Rok Do · Heung Moon Chang · Min Hee Ryu · Kyung Hee Lee · Yeul Hong Kim · Dae Sik Hong · Jae Yong Cho · Kyoung Eun Lee · Si Young Kim

Received: 30 October 2007 / Accepted: 3 December 2007 / Published online: 3 January 2008

Abstract
Purpose This open-label, multicenter phase II study was conducted to investigate the efficacy and safety of capecitabine plus gemcitabine combination chemotherapy as first-line treatment in patients with locally advanced or metastatic pancreatic cancer.
Patients and methods We enrolled 63 patients who received capecitabine 830 mg/m^2 orally twice daily on days 1–21 plus gemcitabine 1000 mg/m^2 as a 30-min infusion on days 1, 8 and 15 every 4 weeks for up to six cycles.
Results A total of 14 patients had partial responses giving an overall response rate of 22% (95% confidence interval [CI] 13–34%) in the intent-to-treat population. The median time to progression and overall survival were 3.9 months (95% CI 3.5–5.7) and 7.5 months (95% CI 5.0–10.0), respectively, and 1-year survival rate was 27.1% in the intent-to-treat population. Capecitabine plus gemcitabine was well tolerated. Grade 3 hematological adverse events were neutropenia (21%) and thrombocytopenia (2%); the only grade 4 hematological events were anemia (2%) and neutropenia (6%). Non-hematological adverse events were mainly gastrointestinal events and hand–foot syndrome, which affected 16% of patients. Grade 3/4 non-hematological events were infrequent.
Conclusion The combination of capecitabine plus gemcitabine appears to be active and well tolerated as first-line treatment in patients with advanced/metastatic pancreatic cancer.

Keywords Pancreatic cancer · Capecitabine · Gemcitabine · Chemotherapy

Introduction

Pancreatic adenocarcinoma is one of the most lethal forms of cancer. It has a mortality rate of 65% within 6 months of diagnosis, which increases to more than 90% 1 year after

H. S. Song · Y. R. Do
Division of Hematooncology,
Department of Internal Medicine, Dongsan Medical Center,
Keimyung University School of Medicine, Dongsan-Dong,
Chung-Gu, Daegu 200-712, South Korea
e-mail: shs7436@dsmc.or.kr

H. M. Chang · M. H. Ryu
Department of Internal Medicine, Asan Medical Center,
University of Ulsan, Seoul, South Korea

K. H. Lee
Department of Internal Medicine,
YeungNam University Medical Center, Daegu, South Korea

Y. H. Kim
Department of Internal Medicine,
Korea University Anam Hospital, Seoul, South Korea

D. S. Hong
Department of Internal Medicine,
SoonChunHyang University Hospital,
Seoul, South Korea

J. Y. Cho
Department of Internal Medicine,
YongDong Severance Hospital, Seoul, South Korea

K. E. Lee
Department of Internal Medicine,
Ewha Womans University Mokdong Hospital,
Seoul, South Korea

S. Y. Kim (✉)
Department of Internal Medicine,
KyungHee University Hospital, Seoul, South Korea
e-mail: sykim55@chol.com

diagnosis [1, 2]. Pancreatic cancer accounted for nearly 3% of all cancers reported in Korea in 2001 [3]. Effective treatment options for patients with non-resectable or metastatic pancreatic carcinoma remain limited. Reported objective response rates are in the range of 0–26% with single-agent chemotherapy and 0–30% with combination chemotherapy, with a median survival duration of 3–6 months for metastatic and 6–10 months for locally advanced pancreatic cancer [4]. Clearly, more effective therapy is needed in the treatment of advanced pancreatic carcinoma.

Since 1997, gemcitabine has been the most widely used chemotherapeutic agent in advanced pancreatic cancer. It achieves significantly better symptom control in advanced pancreatic cancer than 5-fluorouracil (5-FU) [5]. However, despite these improvements, gemcitabine monotherapy has obvious limitations in advanced pancreatic cancer, and various combinations with other agents have been investigated. Capecitabine (Xeloda®, F. Hoffmann La-Roche), an oral fluoropyrimidine that mimics a continuous infusion of 5-FU, is metabolized to 5-FU preferentially by tumor cells, resulting in high intratumoral 5-FU concentrations [6, 7]. The main adverse effects associated with capecitabine are diarrhea and hand–foot syndrome (HFS). Hematological toxicity is uncommon and occurs less frequently with capecitabine than intravenous (iv) bolus 5-FU [8]. A phase II study of capecitabine in patients with metastatic pancreatic cancer revealed an overall response rate of 10%, while 41% of patients had stable disease; in addition, clinical benefit was demonstrated in 24% of patients [9].

The combination of gemcitabine and capecitabine is attractive since the drugs have different mechanisms of action and non-overlapping toxicities. Furthermore, the combination is more convenient to use than 5-FU-based therapy, as capecitabine is administered orally. The combination of capecitabine and gemcitabine has been evaluated in two phase I/II studies [10, 11] using a dose schedule (gemcitabine 1000 mg m^2 given on days 1 and 8 and capecitabine 650 mg m^2 given twice daily on days 1–14 of a 21-day cycle) recommended from an earlier phase I study [10, 12].

We performed a multicenter, phase II trial in order to evaluate the efficacy and tolerability of gemcitabine plus capecitabine in previously untreated patients with inoperable locally advanced or metastatic pancreatic cancer. We used the dosage schedule recommended by Schilsky et al. [12] in their dose-escalation study.

Patients and methods

Patients

Patients with histopathologically proven advanced pancreatic cancer with locally advanced or metastatic disease with measurable lesions were eligible for the study. Other eligibility criteria included: age 18–75 years; Karnofsky performance status ≥70; estimated life expectancy of more than 3 months; adequate renal (serum creatinine ≤1.5 mg dl^{-1}) and liver function (serum bilirubin <1.5 × upper limit of normal (ULN); ALT and AST ≤2.5 × ULN or ≤5 × ULN in cases of liver involvement); and adequate bone marrow reserve (neutrophils ≥1.5 × 10^9 l^{-1}, platelet count ≥100 × 10^9 l^{-1}). If the patients had received previous cancer treatment (e.g. tumor resection or radiotherapy), it had to be discontinued for at least 4 weeks before entry into the study. The study was approved by the institutional review board at each centre and was conducted in accordance with the Declaration of Helsinki (October 2000). All patients provided written informed consent.

Exclusion criteria were as follows: prior chemotherapy for the pancreatic cancer; prior radiotherapy to the target lesion(s) being measured in the study; major surgery or radiotherapy within 4 weeks prior to the start of treatment; severe heart disease; active infection; pregnant or lactating women; prior unanticipated severe reaction(s) to fluoropyrimidine therapy or known dihydropyrimidine dehydrogenase deficiency; metastases involving the central nervous system; severe neurological impairment or mental disorder; active concomitant malignancy; a lack of physical integrity of the upper gastrointestinal tract or malabsorption syndrome; inability to swallow pills; any other serious medical conditions.

Study design and treatment

This trial was an open-label, single-arm, multicenter, phase II study conducted to investigate the efficacy and safety of capecitabine plus gemcitabine combination chemotherapy in patients with locally advanced or metastatic pancreatic cancer. All laboratory tests required to assess eligibility had to be completed within 7 days prior to the start of treatment. Capecitabine was administered orally at a dose of 830 mg m^2 twice daily after a meal on days 1–21 of a 28-day cycle. Gemcitabine 1,000 mg m^2 was administered as a 30-minute iv infusion on days 1, 8 and 15 of each cycle. Patients who responded to treatment (complete or partial response) or whose disease remained stable and who were tolerating chemotherapy were treated for up to six cycles (24 weeks). Thereafter, patients who were responding or in stable disease were continued to be followed until disease progression. These patients continued to receive capecitabine and gemcitabine off-study at the discretion of the investigator. Any additional treatment after disease progression was left to the discretion of the treating physician.

Dose-adjustment criteria were based on hematological parameters and the severity of non-hematological toxicities including HFS. If grade 2, 3 or 4 adverse events occurred,

treatment was interrupted until the adverse effects resolved to grade 0–1. Adverse events were graded according to the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) scale (version 2.0).

Pretreatment and follow-up study

Before study entry, all patients gave a full medical history and underwent a physical examination. A complete blood count with differential was performed and electrolyte and creatinine levels were measured. Biochemical tests and urinalysis were performed. Electrocardiograms, chest X-rays and computed tomographic (CT) scans of the abdomen were performed at baseline in all patients within 2 weeks before starting treatment. Additional imaging investigations were performed if clinically indicated or for further disease measurement.

A complete blood count with differential was performed weekly during all the cycles, serum chemistry was performed, and creatinine and electrolyte levels were measured at each cycle. CT scanning and imaging of measurable disease to assess tumor response were performed every two cycles. At the completion of the study, all clinical, laboratory, radiological imaging and other evaluations were repeated. After completion of the study, the patients underwent follow-up every 3 months until death.

Assessment of efficacy and safety

Tumor responses were evaluated according to the Response Evaluation Criteria in Solid Tumor (RECIST) criteria [13]. All responses had to be maintained for at least 4 weeks and be confirmed by an independent panel of radiologists. The response rate was defined as the sum of the complete plus partial responses. Safety and tolerability were assessed by monitoring adverse events, premature withdrawals, clinical laboratory tests, vital signs, physical measurements and deaths throughout the whole study treatment period and follow-up period.

Analysis of efficacy was performed on the intent-to-treat populations. The intent-to-treat population was defined as all patients who received at least one dose of capecitabine or gemcitabine. Analysis of safety was performed on the safety population, which was defined as all patients who received at least one dose of study medication and for whom follow-up safety information was available.

Statistical analysis

The trial was conducted using Ensign's three-stage design approach, which provides three opportunities for early stopping in case of poor efficacy when $n = 16$, $n = 35$ and $n = 56$ [14]. The stopping rules were designed to help ensure that the trial would be stopped early if the true response rate was $\leq 5\%$ and that the trial would continue if the true response rate was $\geq 15\%$. The three-stage plan adopted provided 80% power at the 0.05 level to distinguish between the null and alternative hypothesis with two opportunities for early stopping in case of poor efficacy.

The primary endpoint of this study was efficacy as determined by the response rate and the secondary endpoints were overall survival (OS) and tolerability. Duration of response was calculated from the day a response was first demonstrated until progressive disease. The time to progression (TTP) was calculated from the day of entry into the study until documented disease progression. OS was calculated from the day of enrolment until death. The median probability of survival and the median TTP were estimated using the Kaplan–Meier method. Confidence intervals (CI) for response rates were calculated using methods for the exact binomial confidence interval.

Results

Patient characteristics

From March 2003 until May 2004, 63 patients were enrolled in this multicenter trial. All 63 patients were included in the safety and intent-to-treat analyses, and 3 patients were excluded because they did not receive 50% of the anticipated capecitabine dose during the first cycle.

Patient characteristics are shown in Table 1. The mean age was 59.5 (range 38–75) years. Locally advanced

Table 1 Patient characteristics

Characteristic	Number of patients $n = 63$ (%)
Age (years)	
Median (range)	59.5 (38–75)
Karnofsky performance status	
100	8 (13)
90	23 (37)
80	25 (40)
70	7 (10)
Gender (male/female)	38/25 (60/40)
Stage of disease	
Locally advanced	21 (33.3%)
Metastatic	42 (66.7%)
Site of metastases	
Liver	33 (52)
Lymph nodes	25 (40)
Peritoneal	4 (6)
Lung	4 (6)

disease was found in 21 (33.3%) and metastatic disease in 42 patients (66.7%). The most common metastatic site was the liver (52%). Nine (14%) patients had previously undergone surgical procedures related to pancreatic cancer; pancreatico-duodenectomy was the most common procedure ($n = 5$). At enrolment, 31 (56%) patients had abdominal pain and all were receiving opioid analgesics.

Treatment compliance

Patients received a total of 251 cycles of chemotherapy (median 4.0 cycles, range 1–6). A total of 26 (41%) patients received both agents for at least five cycles. The mean proportion of the prescribed dose taken was good (>75% for each cycle) for both capecitabine and gemcitabine.

Response to treatment

There were no complete responses to gemcitabine and capecitabine combination therapy (Table 2). There were 14 (22%; 95% CI 13–34%) partial responses in the intent-to-treat population ($n = 63$) at all sites of the disease. Thirty (48%) patients had stable disease and 16 (25%) had progressive disease in the intent-to-treat (ITT) population.

In the ITT population, the median duration of response was 4.9 months (95% CI 3.7–7.2 months) and median TTP was 3.9 months (95% CI 3.5–5.7 months). The median time to treatment failure was 3.3 months (95% CI 2.3–5.5 months). The median OS time was 7.5 months (95% CI 5.0–10.0 months; Fig. 1), and the 1-year survival rate was 27.1%. The median OS time was 9.5 months (95% CI 4.3–14.7 months) for locally advanced disease and 7.2 months (95% CI 5.6–8.8 months) for metastatic disease; this was not statistically significant ($P = 0.319$).

Safety

All 63 patients were evaluated for safety. Commonly observed adverse events during chemotherapy are shown in Table 3. Thrombocytopenia occurred in 25 (40%) patients, but grade 3 events were reported in only one patient; 13 (21%) and 4 (6%) patients presented with grade 3 and 4 neutropenia, respectively. Two (3%) patients developed febrile neutropenia, which required hospitalization in both cases. Gastrointestinal adverse events, such as constipation, nausea/vomiting, asthenia, diarrhea, anorexia and abdominal pain, were common, but grade 3/4 events occurred infrequently and affected only 2–8% of patients (Table 3). HFS occurred in 10 (16%) patients, but grade 3/4 HFS was not observed.

Table 2 Response to treatment

Response	Intent-to-treat population ($n = 63$)
Complete response	0
Partial response	14 (22 %)
Stable disease	30 (48 %)
Progressive disease	16 (25 %
Response rate	22%
Confidence interval, 95%	13–34%

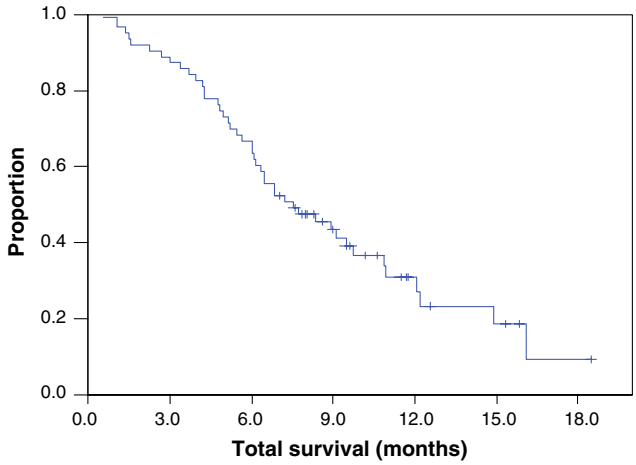

Fig. 1 Kaplan–Meier survival estimates of overall survival ($n = 63$)

Table 3 Adverse events ($n = 63$)

Total, 251 cycles	All grades (%)	Grade 3 (%)	Grade 4 (%)
Hematological			
Anemia	2 (3)	0	1 (2)
Neutropenia	17 (27)	13 (21)	4 (6)
Thrombocytopenia	25 (40)	1 (2)	0
Non-hematological			
Constipation	27 (43)	4 (6)	0
Nausea	26 (41)	2 (3)	0
Vomiting	26 (41)	2 (3)	0
Asthenia	23 (37)	5 (8)	1 (2)
Diarrhea	19 (30)	0	1 (2)
Anorexia	17 (27)	3 (5)	0
Abdominal pain	14 (22)	1 (2)	0
Pyrexia	14 (22)	2 (3)	1 (2)
Pruritis	11 (17)	1 (2)	0
Hand–foot syndrome	10 (16) 16	0	0
Fatigue	7 (11)	1 (2)	0

Discussion

The current standard regimen for patients with advanced pancreatic cancer is single-agent gemcitabine [5]. Even

though gemcitabine has shown marginal objective activity in patients with pancreatic cancer, the drug is now considered the treatment of choice for this disease because it improves quality of life and offers clinical benefit for a high percentage of patients [15]. Combination regimens of gemcitabine and 5-FU are well tolerated and are as effective as gemcitabine monotherapy with an observed response rate of 19% and a median progression-free survival of 7.4 months [16, 17].

Capecitabine and gemcitabine have demonstrated synergistic activity in preclinical studies based on a xenograft model [18]. However, to date, published clinical data concerning the combination of gemcitabine and capecitabine in pancreatic cancer remain limited. A recent phase I/II trial recommended that the dose schedule for phase II studies should be gemcitabine 1,000 mg m^2 given on days 1 and 8 and capecitabine 650 mg m^2 given twice daily on days 1–14 of a 21-day cycle [10]. In 27 patients with measurable disease, they observed one complete and four partial responses with the recommended dosage schedule giving an overall response rate of 19%. Another phase II trial using the same dose schedule reported a similar response rate of 19% with a median OS of 8 months [11]. In the present study, we used the slightly more dose-intense regimen identified by Schilsky et al. [12] in which gemcitabine 1,000 mg m^2 is administered on days 1, 8 and 15 and capecitabine 830 mg m^2 twice daily on days 1–21 of a 28-day cycle. With this regimen, we observed a slightly higher response rate of 22% and a median OS of 7.5 months. The results of the present study suggest that the combination of gemcitabine and capecitabine is a relatively active and well-tolerated regimen for the treatment of patients with pancreatic cancer. Indeed, the 22% objective response rate, which corresponds to 14 partial responses, and the median OS of 7.5 months are acceptable for this patient group that has a poor prognosis.

In addition to these data from phase II studies, a statistically significant survival advantage was obtained in a large phase III study comparing the combination of gemcitabine plus capecitabine with gemcitabine monotherapy for the treatment of advanced pancreatic cancer conducted in the UK [19]. An interim analysis of this study showed that median survival was 7.4 months for the combination compared with 6 months for gemcitabine monotherapy. In addition, 1-year survival rates were 26 and 19%, respectively. The investigators concluded that there was a significant improvement in OS with gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer and that the regimen was associated with acceptable levels of toxicity.

Adverse events observed in the present study, particularly neutropenia and thrombocytopenia, were more common than in the study by Hess et al. [10], but grade 3/4 adverse events remained rare. The higher rate of hematological adverse events can probably be explained by the higher dose of capecitabine used in the present study (830 versus 650 mg m^2 twice daily) and the longer treatment period (three versus two doses of gemcitabine and 21 versus 14 days of capecitabine).

There are several other strategies, which may help to improve the therapeutic management of patients with advanced pancreatic cancer, namely modified administration schedules or dose intensification of gemcitabine [20, 21]. Another possibility to enhance the antitumor potential of gemcitabine may be to combine it with other active cytotoxic drugs, for example S-1 or erlotinib [22, 23]. S-1 is a new oral fluorinated pyrimidine, which contains tegafur, 5-chloro 2,4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo) in a molar ratio of FT:CDHP:Oxo = 1:0.4:1. The administration of oral S-1 is more convenient and stimulates the effect of 5-FU. In a phase II study of S-1 and gemcitabine combination (S-1 30 mg/m^2 bid for 14 consecutive days and gemcitabine 1,000 mg/m^2 on day 8 and 15, repeated every 21 days), the result was very promising (response rate 48%, median time to progression 5.4 months, overall survival 12.5 months, and 1-year survival rate 54%) [22]. Future prospective randomized clinical trial is needed to evaluate the survival benefit in comparison with gemcitabine monotherapy. In a xenograft model of pancreatic cancer, the extent of apoptosis was significantly increased by the addition of erlotinib to gemcitabine [23]. Recently presented data from a phase III trial of the National Cancer Institute of Canada Clinical Trials Group in advanced pancreatic cancer revealed significant prolongation of survival with the combination of gemcitabine plus erlotinib compared to gemcitabine monotherapy (overall survival 6.24 months versus 5.91 months, $P = 0.025$; 1-year survival rate 23% versus 17%, $P = 0.023$) [24].

In conclusion, the combination of capecitabine and gemcitabine is an active regimen for patients with pancreatic cancer, yielding a 22% objective response rate, which is higher than that achieved with either drug alone. This combination is associated with an improvement in tumor-related symptoms in a substantial proportion of patients and with an acceptable median survival. In addition, the regimen not only has a favourable toxicity profile, but is also convenient for the patient. Further clinical research efforts, including the testing of combination therapy with other conventional anticancer drugs and/or biologicals are encouraged to improve therapeutic options in advanced pancreatic cancer.

Acknowledgments This study was supported by a grant from ROCHE Korea.

References

1. Kelly DM, Benjamin IS (1995) Pancreatic carcinoma. Ann Oncol 6:19–28

2. Niederhuber JE, Brennan MF, Menck HR (1995) The national cancer database reports on pancreatic cancer. Cancer 76:1671–1677
3. Korean National Cancer Center (2001) Korean central cancer registry 22nd annual report. Available from http://www.ncc.re.kr
4. Hawes RH, Xiong Q, Waxman I, Chang KJ, Evans DB, Abbruzzese JL (2000) A multispecialty approach to the diagnosis and management of pancreatic cancer. Am J Gastroenterol 95:17–31
5. Burris HA III, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD, Von Hoff DD (1997) Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 15:2403–2413
6. Miwa M, Ura M, Nishida M, Sawada N, Ishikawa T, Mori K, Shimma N, Umeda I, Ishitsuka H (1998) Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. Eur J Cancer 34:1274–1281
7. Schüller J, Cassidy J, Dumont E, Roos B, Durston S, Banken L, Utoh M, Mori K, Weidekamm E, Reigner B (2000) Preferential activation of capecitabine in tumor following oral administration to colorectal cancer patients. Cancer Chemother Pharmacol 45:291–297
8. Cassidy J, Twelves C, van Cutsem E, Hoff P, Bajetta E, Boyer M, Bugat R, Burger U, Garin A, Graeven U, McKendrick J, Maroun J, Marshall J, Osterwalder B, Pérez-Manga G, Rosso R, Rougier P, Schilsky RL, on behalf of the Capecitabine Colorectal Cancer Study Group (2002) First-line oral capecitabine therapy in metastatic colorectal cancer: a favorable safety profile compared with intravenous 5-fluorouracil/leucovorin. Ann Oncol 13:566–575
9. Cartwright TH, Cohn A, Varkey JA, Chen YM, Szatrowski TP, Cox JV, Schulz JJ (2002) Phase II study of oral capecitabine in patients with advanced or metastatic pancreatic cancer. J Clin Oncol 20:160–164
10. Hess V, Salzberg M, Borner M, Morant R, Roth AD, Ludwig C, Herrmann R (2003) Combining capecitabine and gemcitabine in patients with advanced pancreatic carcinoma: a phase I/II trial. J Clin Oncol 21:66–68
11. Stathopoulos GP, Syrigos K, Polyzos A, Fountzilas G, Rigatos SK, Ziras N, Potamiannou A, Tsiakopoulos I, Androulakis N, Aravantinos G, Athanasiadis A, Papakotoulas P, Georgoulias V (2004) Front-line treatment of inoperable or metastatic pancreatic cancer with gemcitabine and capecitabine: an intergroup, multicenter, phase II study. Ann Oncol 15:224–229
12. Schilsky RL, Bretucci D, Vogelzang NJ, Kindler HL, Ratain MJ (2002) Dose-escalating study of capecitabine plus gemcitabine combination therapy in patients with advanced cancer. J Clin Oncol 20:582–587
13. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG (2000) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205–216
14. Ensign LG, Gehan EA, Kamen DS, Thall PF (1994) An optimal three-stage design for phase II clinical trials. Stat Med 13:1727–1736
15. Casper ES, Green MR, Kelsen DP, Heelan RT, Brown TD, Flombaum CD, Trochanowski B, Tarassoff PG (1994) Phase II trial of gemcitabine (2,2′-difluorodeoxycytidine) in patients with adenocarcinoma of the pancreas. Invest New Drugs 12:29–34
16. Hidalgo M, Castellano D, Paz-Ares L, Gravalos C, Diaz-Puente M, Hitt R, Alonso S, Cortes-Funes H (1999) Phase I-II study of gemcitabine and fluorouracil as a continuous infusion in patients with pancreatic cancer. J Clin Oncol 17:585–592
17. Oettle H, Arning M, Pelzer U, Arnold D, Stroszczynski C, Langrehr J, Reitzig P, Kindler M, Herrenberger J, Musch R, Korsten FW, Huhn D, Riess H (2000) A phase II trial of gemcitabine in combination with 5-fluorouracil (24-hour) and folinic acid in patients with chemonaive advanced pancreatic cancer. Ann Oncol 11:1267–1272
18. Ren Q, Kao V, Germ JL (1998) Cytotoxicity and DNA fragmentation associated with sequential gemcitabine and 5-fluoro-2-deoxyuridine in HT-29 colon cancer cells. Clin Cancer Res 4:2811–2818
19. Cunningham D, Chau I, Stocken D, Davies C, Dunn J, Valle J, Smith D, Steward W, Harper P, Neoptomos J (2005) Phase III randomised comparison of gemcitabine (GFM) versus gemcitabine plus capecitabine (GEM-CAP) in patients with advanced pancreatic cancer. Eur J Cancer 3(supplement):12(PS12)
20. Scheithauer W, Schull B, Ulrich-Pur H, Schmid K, Raderer M, Haider K, Kwasny W, Depisch D, Schneeweiss B, Lang F, Korneck GV (2003) Biweekly high-dose gemcitabine alone or in combination with capecitabine in patients with metastatic pancreatic adenocarcinoma: a randomized phase II trial. Ann Oncol 14:97–104
21. Tempero M, Plunkett W, van Ruiz Haperen V, Hainsworth J, Hochster H, Lenzi R, Abbruzzese J (2003) Randomized phase II comparison of dose-intense gemcitabine: thirty-minute infusion and fixed dose rate infusion in patients with pancreatic adenocarcinoma. J Clin Oncol 21:3402–3408
22. Nakamura K, Yamaguchi T, Ishihara T, Kobayashi A, Tadenuma H, Sudo K, Kato H, Saisho H (2005) Phase I trial of oral S-1 combined with gemcitabine in metastatic pancreatic cancer. Br J Cancer 92:2134–2139
23. Ng SS, Tsao MS, Nicklee T, Hedley DW (2002) Effects of the epidermal growth factor receptor inhibitor OSI-774, Tarceva, on downstream signaling pathways and apoptosis in human pancreatic adenocarcinoma. Mol Cancer Ther 1:777–783
24. Moore MJ, Glodstein D, Hamm J, Figer A, Hecht JR, Gallinger S, Au HJ, Murawa P, Walde D, Wolff RA, Campos D, Lim R, ing K, Clark G, Voskoglou-Nomikos T, Ptasynski M, Parulekar W, National Cancer Institute of Canada Clinical Trials Group (2007) Erlotinib plus gemcitabine compared gemcitabine alone in patients with advanced pancreatic cancer: a III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 20:1960–1966