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ORIGINAL ARTICLE

Phase II study of biweekly gemcitabine followed by oxaliplatin and simplified 48-h infusion of 5-fluorouracil/leucovorin (GOFL) in advanced pancreatic cancer

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Abstract
Purpose To evaluate the efficacy and safety profile of a triplet regimen consisting of gemcitabine, oxaliplatin, and infusional fluorouracil and leucovorin (LV) in advanced pancreatic carcinoma (APC).
Patients and methods Chemotherapy-naïve patients with histo-/cytologically proven unresectable APC, and bi-dimensionally measurable diseases were eligible. Treatment consisted of fixed-dose rate (10 mg/m^2/min) infusion of 800 mg/m^2 gemcitabine followed by 2-h infusion of 85 mg/m^2 oxaliplatin and then 48-h infusion of fluorouracil and LV (3,000 and 300 mg/m^2, respectively) every 2 weeks (the GOFL regimen). The primary end-point was objective response rate.
Results Forty-five patients were enrolled and received a median of seven [95% confidence interval (CI) 6.4–8.8] cycles of treatment. On intent-to-treat analysis, the overall response and disease-control rates were 33.3% (95% CI 21.4–48.0%) and 68.9% (95% CI 54.8–83.0%), respectively. Clinical benefit response was observed in 46.2% of initially symptomatic patients. The median time-to-tumor progression and overall survival were 5.1 (95% CI 4.0–6.3) months and 8.7 (95% CI, 6.1–11.3) months, respectively. Major grade 3–4 toxicities were neutropenia (28.9%, with

This article describes the triplet regimen, GOFL (Gemcitabine, Oxaliplatin, Fluorouracil, Leucovorin), being feasible and exhibiting promising activity against advanced pancreatic cancer. This phase II study revealed that GOFL might have better therapeutic efficacy and toxicity profile compared to the current standard gemcitabine monotherapy.

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4.4% complicated with fever), peripheral sensory neuropathy (15.6%), nausea/vomiting (13.3%), and diarrhea (6.7%).

Conclusions The triplet regimen is feasible and exhibits promising activity against APC, deserving further exploration.

Keywords Gemcitabine · Oxaliplatin · Fluorouracil · Pancreatic cancer · Phase II

Introduction

Pancreatic cancer is one of the most detrimental malignancies with only 10–15% of the patients being able to undergo curative intent surgery at the time of diagnosis. Although chemotherapy has been shown to improve both survival and quality of life compared with best supportive care alone in patients with advanced pancreatic carcinoma (APC), the therapeutic results of the current standard gemcitabine monotherapy remain largely unsatisfactory [1–3].

In the past decade, various gemcitabine-based doublets (gemcitabine combined with either another cytotoxic agent or a molecular targeting agent) have been extensively investigated in an attempt to improve the clinical outcomes of APC patients. Unfortunately, most of them failed to achieve definitive, clinically relevant survival benefits over gemcitabine monotherapy in randomized phase III trial settings. However, meta-analysis shows that adding either a fluoropyrimidine or a platinum analog to gemcitabine provides a significant survival benefit over gemcitabine monotherapy for APC patients [4].

Recently, European investigators and our group have shown that gemcitabine plus intermittent infusion of fluorouracil (5-FU) with leucovorin (LV) modulation, given either weekly or biweekly, could achieve consistent 19–23% of overall response rates (ORR) and/or 6.9–9.0 months of median overall survival (OS) in phase II settings. These results seemed superior to the 14% and 4.4 months achieved with gemcitabine plus bolus 5-FU in the ECOG E3296 study, a regimen used in the ECOG E2297 phase III study [5–8]. The favorable toxicity profile of the gemcitabine plus LV-modulated infusional 5-FU regimen implies that a triplet regimen combining a third, potentially active, non-cross-resistant agent into such gemcitabine plus LV-modulated infusional 5-FU doublets might be a feasible strategy to improve the therapeutic efficacies of chemotherapy in APC [5, 8].

Oxaliplatin, a third-generation platinum analog, has been shown to exhibit activity against pancreatic cancer cells and to enhance the cytotoxicity of both 5-FU and gemcitabine against colon cancer cells in vitro [9, 10]. Clinically, the combinations of gemcitabine plus oxaliplatin (i.e., the GEMOX regimen), and oxaliplatin plus infusional 5-FU with LV modulation have been shown to be active in chemotherapy-naïve and gemcitabine-refractory APC [11–15]. Based on these data, we had conducted a phase I trial to evaluate the feasibility of a triplet regimen consisting of biweekly gemcitabine followed by oxaliplatin and a 48-h infusion of 5-FU and LV (the GOFL regimen) in APC patients [16]. The recommended dose of oxaliplatin was determined as 85 mg/m^2. Herein, we report the efficacy and safety profile of the GOFL regimen as first-line treatment in APC.

Patients and methods

Patient selection

Patients with histo-/cytologically proven unresectable, locally advanced, recurrent or metastatic APC were eligible. The inclusion criteria included age ≤75 years; Eastern Cooperative Oncology Group performance scores (ECOG PS) ≤2; WBC ≥3,000 μl^{-1}; absolute neutrophil count ≥1,500 μl^{-1}; platelet count ≥100,000 μl^{-1}; bilirubin ≤2.0 mg/dl; AST and alkaline phosphatase levels ≤5 times the institutional upper limit; creatinine ≤1.5 mg/dl; and negative pregnancy test for women with childbearing potential. Exclusion criteria included prior chemotherapy, uncontrolled infections, severe cardiopulmonary debilitating illness, sensory neuropathy of grade ≥1 of any etiology, and central nervous system metastases. A minimum of 4 weeks after prior surgery or radiotherapy was required. All patients gave their signed informed consent. The study was approved by the institutional review board of participating hospitals and by the Department of Health, Executive Yuen, Taiwan and has been submitted for registration with ClinicalTrials.gov, number NCT00154791.

Treatment plan

The treatment consisted of a fixed-dose rate (FDR, at 10 mg/m^2/min) infusion of 800 mg/m^2 gemcitabine (Gemzar®, Eli Lilly and Co., Indianapolis, IN, USA), followed by a 2-h infusion of 85 mg/m^2 oxaliplatin (Oxalip®, kindly supplied by TTY Biopharm Co. Ltd, Taipei, Taiwan), and then a 48-h infusion of 5-FU and LV (3,000 and 300 mg/m^2, respectively, mixed in 250–500 ml of normal saline) given via a central venous catheter. The treatment was given every 2 weeks as one cycle. Anti-emetics consisted of an intravenous bolus injection of dexamethasone and 5-hydroxytryptamine-3-receptor inhibitors. Prophylactic granulocyte-colony stimulating factor was not allowed until the presence of grade 4 or complicated neutropenia in the prior cycle of treatment.

Evaluations

A detailed history evaluation, physical examination, and complete blood count with differential classification were performed before each cycle of treatment, while blood biochemistry was checked every 4 weeks. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0 [17]. Computed tomography was performed before treatment and after every four cycles of chemotherapy to evaluate tumor response. Tumor response was evaluated according to response criteria of the World Health Organization (WHO) [18]. Complete response was defined as the complete disappearance of all assessable disease, and partial response (PR) was defined as a ≥50% decrease of the sum of the products of the diameters of measurable lesions. Responses were confirmed by repeated assessments performed >4 weeks apart. Stable disease (SD) was defined as a <50% reduction or <25% increase in the sum of the products of the diameters of measurable lesions for a minimum of 8 weeks or a response that lasted <4 weeks. Progressive disease (PD) was defined as the appearance of new lesions or a >25% increase in area(s) of original measurable disease.

Dose modification

Chemotherapy was given only when pre-treatment laboratory data showing WBC ≥3,000 μl^{-1} and platelet count ≥100,000 μl^{-1} as well as all non-hematological adverse events recovered to no greater than grade 1. In the presence of grade ≥2 sensory neuropathy, oxaliplatin would be omitted and only gemcitabine and 5-FU/LV would be given afterward. In the presence of grade-4 thrombocytopenia, febrile neutropenia, unmanageable grade 3–4 non-hematological toxicities, or delayed recovery of adverse event for >2 weeks, the dose of oxaliplatin would be reduced by 25% in subsequent cycles of treatment. If the above toxicities occurred after oxaliplatin dose modification, 5-FU doses would be reduced by 25% in subsequent treatments. Patients would be off-studied in the presence of persistent grade 3–4 toxicity after dose reduction of both oxaliplatin and 5-FU, PD, unacceptable toxicities, and patients' refusal or death.

Clinical benefit assessment

Clinical benefit response (CBR) was defined according to the criteria previously described by Burris et al. [3]: changes in pain (pain intensity and analgesic consumption), performance score and body weight were used to classify patients as responders or non-responders. CBR would be determined for patients who were symptomatic (ECOG PS >1, BW loss ≥10%, and/or tumor-related pain requiring analgesic/narcotics) at enrollment.

Statistical considerations

The primary end-point of the study was ORR. Secondary end-points were time-to-tumor progression (TTP), and OS. All efficacy calculations were based on intent-to-treat (ITT) analyses. According to Simon's optimal two-stage design with uninterested and interested ORR of 15 and 30%, respectively, and both α and β errors probabilities of 0.10, 21 patients would be recruited at first. If less than three responders were observed among the first 21 evaluable patients, then the trial would be terminated, otherwise, if greater than three responders were observed, an additional 24 patients would be accrued onto the second stage of the study. If ≥13 responses were observed among all 45 evaluable patients, the triplet regimen would be considered effective; otherwise, we would conclude that the GOFL regimen was not effective enough for further exploration. The 95% confidence interval (CI) for response would be calculated. TTP and OS were calculated from the starting date of treatment to the first evidence of disease progression, and to death or last follow-up visit, respectively, and estimated by the Kaplan–Meier method [19].

Results

Patient characteristics, study treatment, and drug delivery

From May 2003 to September 2005, 45 patients were accrued whose demographic characteristics are listed in Table 1.

A total of 342 cycles were given, with a median of seven (95% CI 6.4–8.8) cycles per patient. Dose reductions, short treatment delays (≤7 days), and longer delays (>7 days) were required in 114 (33.3%), 85 (24.9%), and 20 (5.8%) cycles, respectively. The delivered, relative dose intensities of gemcitabine, oxaliplatin, and 5-FU were 87.5, 84.2, and 86.5%, respectively.

Objective response and survival

Among the 21 patients accrued into the first-stage of the study, the best tumor response was PR in four and SD in ten patients, including two showing >30% decrease in tumor size. Per protocol, 24 patients were further accrued. Of all 45 patients, the best tumor responses were confirmed PR in 15, SD in 16, and progression disease/un-evaluable in 14. On ITT analysis, the ORR and disease-control rates were 33.3% (95% CI 21.4–48.0%) and 68.9% (95% CI 54.8–83.0%), respectively. In unplanned, post hoc analyses, the ORR was 22.2% (95% CI 0–56.1%) and 36.1% (95% CI 19.6–52.6%) in patients with locally advanced and metastatic/recurrent diseases, respectively ($P = 0.695$, Fisher's

Table 1 Demographic characteristics of patients

	No. of patients	%
Gender		
Male	27	60
Female	18	40
Age (years)		
Median	57	
Range	28–75	
ECOG PS		
0	5	11.1
1	36	80
2	4	8.9
Body weight loss		
None	13	28.9
<10%	13	28.9
≥10%	15	33.3
Medication for pain control		
None	28	62.2
≤NSAID	2	4.4
Analgesic/narcotics	11	24.4
Disease stage		
Locally advanced	9	20
Recurrent/metastatic	36	80
Prior surgery		
None	34	75.6
Curative resection	4	8.9
Palliative bypass	6	13.3
Explorative laparotomy	1	2.2
No. of sites involved		
1	9	20
2	29	64.4
3	4	8.9
≥4	3	6.7
Disease localization		
Pancreas	42	93.3
Liver	30	66.7
Lymph nodes	8	17.8
Peritoneum	1	2.2
Lung	2	4.4
Other	6	13.3

ECOG PS performance score of Eastern Cooperative Oncology Group, *NSAID* non-steroid anti-inflammatory drug

Exact test). Disease-control rate in corresponding group of patients was 77.8 and 64.9%, respectively.

As of 30 June 2007, all but two patients deceased. The median follow-up period was 8.7 (95% CI 6.8–10.7) months. The median TTP and OS were 5.1 (95% CI 4.0–6.3) months and 8.7 (95% CI 6.1–11.3) months, respectively (Figs. 1, 2). The 12-month survival rate was 36%. The

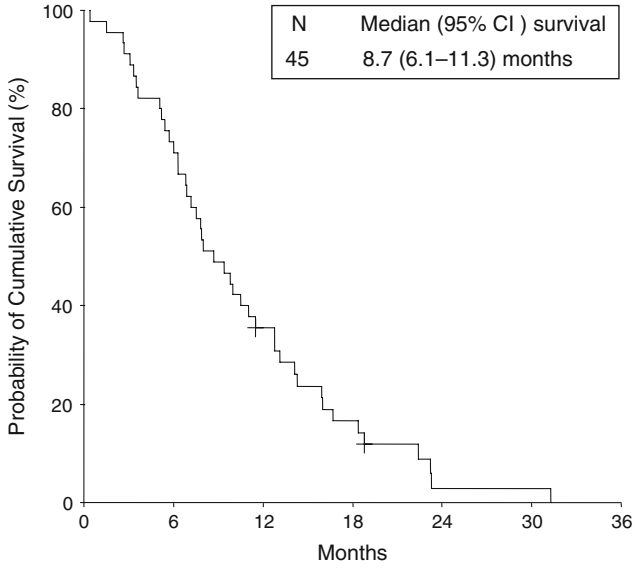

Fig. 1 Kaplan–Meier method estimated survival curves for intent-to-treat patients, overall survival

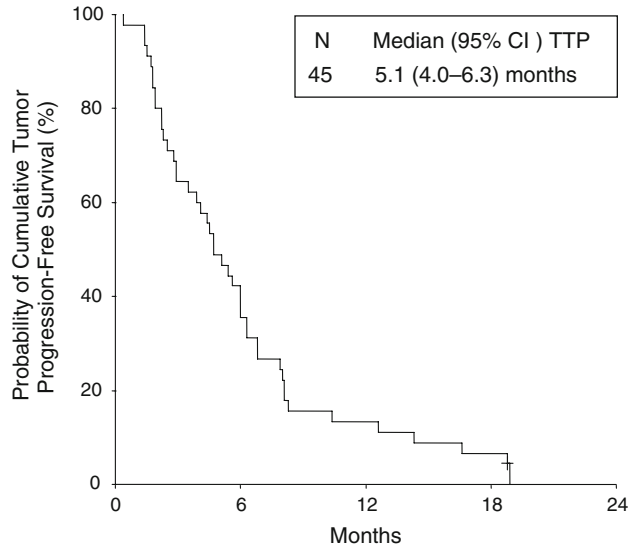

Fig. 2 Kaplan–Meier method estimated survival curves for intent-to-treat patients, time-to-progression

median OS of patients with metastatic/recurrent and locally advanced disease were 7.2 (95% CI 5.7–8.8) months and 15.9 (95% CI 11.3–20.5) months, respectively.

Safety

All treated patients ($n = 45$) were assessed for toxicity. Grade 3–4 toxicities are listed in Table 2 with most common ones being neutropenia (28.9%, with neutropenic fever in 4.4%), nausea/vomiting (13.3%), and diarrhea (6.7%). The 60 days mortality rate was 4.4% (95% CI 1.4–14.8%) due to the incidence of massive upper gastrointestinal bleeding on

Table 2 Main grade 3–4 toxicities related to study treatment

Toxicity	Per patient (n = 45)			
	Grade 3		Grade 4	
	n	%	n	%
Hematologic toxicities				
Neutropenia	9	20	2	4.4
Febrile neutropenia	2	4.4	0	0
Anemia	0	0	0	0
Thrombocytopenia	4	8.8	2	4.4
Non-hematologic toxicities				
Diarrhea	3	6.7	0	0
Nausea	6	13.3	0	0
Vomiting	5	11.1	1	2.2
Asthenia	2	4.4	0	0
Peripheral neuropathy[a]	7	15.6	0	0
Mucositis	2	4.4	0	0
Skin rash	1	2.2	0	0
ALT	1	2.2	0	0
Neurocortical[b]	1	2.2	0	0

[a] Grade 2/3

[b] Hyper-ammonemic encephalopathy

day 13 in one patient and pulmonary embolism on day 44 in the other. Sensory neuropathy of grade 2–3 led to the omission of oxaliplatin from their treatment in seven (15.6%) patients after a median of ten cycles of treatment. In addition, oxaliplatin was discontinued due to allergic reactions in four (8.9%) patients at cycles 6, 7, 8, and 8, respectively.

Clinical benefit response

Among the 26 initially symptomatic patients (ECOG PS >1 in 4, BW loss ≥10% in 15, and/or tumor-related pain requiring analgesic/narcotics in 13), 12 (46.2%) achieved CBR. Reductions in analgesics/narcotics requirement, improvements in ECOG PS and gains of BW ≥7% were observed in 46.2% (6 of 13), 75% (3 of 4), and 33% (5 of 15) of corresponding symptomatic patients, respectively.

Discussion

The rationale for developing this triplet (gemcitabine, oxaliplatin, and infusional 5-FU with LV modulation) regimen was based on earlier observations of a potentially better therapeutic index for gemcitabine plus infusional 5-FU with LV modulation compared to that of gemcitabine plus bolus 5-FU. Furthermore, these three agents showed synergism and have non-overlapping toxicity profile [5–15]. Unfortunately, despite the exciting phase II results, the potential clinical benefits of gemcitabine/oxaliplatin or gemcitabine plus LV-modulated infusional 5-FU combinations over gemcitabine monotherapy in APC have been challenged by the negative results from recently published prospective randomization phase III studies, i.e., the GERCOR/GISCAD and ECOG E6201 studies for GEMOX, and the Charitè Onkologie CONKO-002 study for gemcitabine plus LV-modulated infusional 5-FU [11, 20, 21]. The clinical benefit of a triplet combination incorporating these three agents was called into question.

However, from another point of view, our GOFL regimen is fundamentally a modified FOLFOX4 following FDR infusion of gemcitabine given every 2 weeks. Two randomization studies have recently demonstrated a trend towards improving activity of oxaliplatin plus infusional 5-FU with/without LV modulation over either oxaliplatin monotherapy or infusional 5-FU with LV modulation alone for APC [22, 23]. In a randomization phase II study, Ducreux et al. [22] showed that oxaliplatin plus infusional 5-FU (OXFU) could provide survival benefit over oxaliplatin monotherapy (median OS, 9.0 versus 3.4 months) as first-line therapy for APC patients. Furthermore, in a phase III (CONKO-003) trial, Pelzer et al. [23] demonstrated that adding oxaliplatin to LV-modulated infusional 5-FU could result in a significant improvement in PFS and second-line OS (median OS, 26 versus 13 weeks for LV-modulated infusional 5-FU alone) in gemcitabine-refractory APC.

In our phase II study, the novel triplet regimen, a combination of two active components—FDR infusion of gemcitabine plus modified FOLFOX4, was shown to be feasible and moderately active in APC with an ORR of 33.3% (95% CI 21.4–48.0%) and OS of 8.7 (95% CI 6.1–11.3) months. These results were comparable to those achieved with other triplet chemotherapy regimens in APC, i.e., 29.0% and 8 months for FOLFU GEMOX, and 26% and 10.2 months for Folfirinox [24, 25]. Recently, the high response rate of the Folfirinox regimen has been confirmed by a randomized phase II trial (the ACCORD 11 trial), 31.8 versus 11.4% for gemcitabine. The exciting result has allowed its continuation as a phase III study to evaluate whether the Folfirinox regimen will provide a survival benefit over gemcitabine in patients with metastatic APC [26]. As compared with Folfirinox, our GOFL regimen appears less toxic, with incidence of grade 3–4 neutropenia and diarrhea of 29 versus 52% and 7 versus 17%, respectively [25]. These findings suggest that GOFL might be a more feasible triplet regimen for further exploration in the treatment of rather fragile APC patients.

In the current study, like most other phase II or III trials for chemotherapy ± targeting agent(s) in APC, patients with either locally advanced or metastatic/recurrent diseases were included [27]. Post hoc analysis showed that the ORR and tumor-control rate were similar between the

subgroups of patients with metastatic/recurrent and locally advanced APC, while the median OS was better for patients with locally advanced diseases, as observed in the GERCOR/GISCAD phase III trial and the phase II study of Conroy et al. [11, 25]. Because of limited number of patients with locally advanced diseases in both studies of Conroy et al. and ours (11 and 9 patients, respectively), the confidence interval of efficacies was large for that subpopulation of patients. Although the results were encouraging, they have to be validated by further large-scale prospective studies. Recent retrospective analyses showed that a multimodality approach with incorporation of consolidation CCRT after primary chemotherapy might provide additional survival benefits for patients with locally advanced APC receiving first-line chemotherapy [28, 29]. Based on these observations, a multi-center, phase II trial is ongoing to evaluate the efficacy of induction GOFL followed by gemcitabine-based CCRT in patients with locally advanced APC [30].

In this study, 34 patients experienced grade 3–4 hematologic or non-hematologic toxicities during a median of seven cycles of chemotherapy, which resulted in 114 (33.3%) cycles of dose reduction and 105 (30.7%) delayed cycles. Most of the treatment-related grade 3–4 toxicities were manageable. Compared to gemcitabine/oxaliplatin and gemcitabine plus LV modulated 5-FU combinations, GOFL was associated with higher incidence of grade 3–4 neutropenia (28.9 vs. 11, 20%) and nausea/vomiting (24.4 vs. 14, 10%), but not thrombocytopenia (13.3%), and diarrhea (6.7%) [5, 11]. The 15.6% of grade $\geq$2 peripheral sensory neuropathy was similar to that of GEMOX [11].

In conclusion, the GOFL regimen seemed promising for patients with APC. The 33.3% of ORR, 8.7 months of median OS and 36% of 12 months survival rate were encouraging. Toxicities were mainly hematological and manageable. CBR was observed in 46.2% of patients who were symptomatic at enrollment. Further study to validate the exciting survival results of patients with locally advanced disease is ongoing.

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References

1. Palmer KR, Kerr M, Knowles G et al (1994) Chemotherapy prolongs survival in inoperable pancreatic carcinoma. Br J Surg 81(6):882–885
2. Glimelius B, Hoffman K, Sjoden PO et al (1996) Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer. Ann Oncol 7(6):593–600
3. Burris HA, Moore MJ, Andersen J et al (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(6):2403–2413
4. Heinemann V, Hinke A, Bock S et al (2007) Gemcitabine-based combinations (gem + x) vs Gemcitabine (gem) alone in the treatment of advanced pancreatic cancer: meta-analysis of sixteen randomized trials. J Clin Oncol 25(18S):4515
5. Shiah HS, Cheng AL, Hsu C et al (2006) Phase I–II trial of weekly gemcitabine plus high-dose 5-fluorouracil and leucovorin in advanced pancreatic cancer. J Gastroenterol Hepatol 21(3):531–536
6. Berlin JD, Adak S, Vaughn DJ et al (2000) A phase II study of gemcitabine and 5-fluorouracil in metastatic pancreatic cancer: an Eastern Cooperative Oncology Group Study (E3296). Oncology 58(3):215–218
7. Oettle H, Arning M, Pelzer U et al (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(10):1267–1272
8. Andre T, Noirclerc M, Hammel P et al (2004) Phase II study of leucovorin, 5-fluorouracil and gemcitabine for locally advanced and metastatic pancreatic cancer (FOLFUGEM 2). Gastroenterol Clin Biol 28(8–9):645–650
9. Raymond E, Buquet-Fagot C, Djelloul S et al (1997) Antitumor activity of oxaliplatin in combination with 5-fluorouracil and the thymidylate synthase inhibitor AG337 in human colon, breast and ovarian cancers. Anticancer Drugs 8(9):876–885
10. Faivre S, Raymond E, Woynarowski JM et al (1999) Supraadditive effect of 2′, 2′-difluorodeoxycytidine (gemcitabine) in combination with oxaliplatin in human cancer cell lines. Cancer Chemother Pharmacol 44:117–123
11. Louvet C, Labianca R, Hammel P et al (2005) Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. J Clin Oncol 23(15):3509–3516
12. Demols A, Peeters M, Polus M et al (2006) Gemcitabine and oxaliplatin (GEMOX) in gemcitabine refractory advanced pancreatic adenocarcinoma: a phase II study. Br J Cancer 94(4):481–485
13. Ghosn M, Farhat F, Kattan J et al (2007) FOLFOX-6 combination as the first-line treatment of locally advanced and/or metastatic pancreatic cancer. Am J Clin Oncol 30(1):15–20
14. Gebbia V, Maiello E, Giuliani F et al (2007) Second-line chemotherapy in advanced pancreatic carcinoma: a multicenter survey of the Gruppo Oncologico Italia Meridionale on the activity and safety of the FOLFOX4 regimen in clinical practice. Ann Oncol 18(6S):vi124–127
15. Oettle H, Pelezer U, Stieler J (2005) Oxaliplatin/folinic acid/5-fluorouracil [24 h] (OFF) plus best supportive care versus best supportive care alone (BSC) in second-line therapy of gemcitabine-refractory advanced pancreatic cancer (CONKO 003). J Clin Oncol 23(16S):4031
16. Ch'ang HJ, Wang CC, Cheng AL et al (2006) Phase I study of biweekly gemcitabine followed by oxaliplatin and simplified 48-h infusion of fluorouracil/leucovorin for advanced pancreatic cancer. J Gastroenterol Hepatol 21(5):874–879
17. Trotti A, Byhardt R, Stetz J et al (2000) Common toxicity criteria: version 2.0. An improved reference for grading the acute effects of cancer treatment: impact on radiotherapy. Int J Radiat Oncol Biol Phys 47(1):13–47
18. Miller AB, Hoogstraten B, Staquet M et al (1981) Reporting results of cancer treatment. Cancer 47(1):207–214
19. Kaplan EL, Meier P (1958) Nonparametric estimation from incomplete observation. J Am Stat Assoc 53:457–481
20. Riess H, Helm A, Niedergethmann M et al (2005) A randomized, prospective, multicenter, phase II trial of gemcitabine, 5-fluorouracil (5-FU), folinic acid vs. gemcitabine alone in patients with advanced pancreatic cancer. J Clin Oncol 23(16S):4009

21. Poplin E, Levy DE, Berlin J et al (2006) Phase III trial of gemcitabine (30-minute infusion) versus gemcitabine (fixed-dose-rate infusion [FDR]) versus gemcitabine + oxaliplatin (GEMOX) in patients with advanced pancreatic cancer (E6201). J Clin Oncol 24(18S):4004
22. Ducreux M, Mitry E, Ould-Kaci M et al (2004) Randomized phase II study evaluating oxaliplatin alone, oxaliplatin combined with infusional 5-FU, and infusional 5-FU alone in advanced pancreatic carcinoma patients. Ann Oncol 15(3):467–473
23. Pelzer U, Kubica K, Stieler J et al (2008) A randomized trial in patients with gemcitabine refractory pancreatic cancer. Final results of the CONKO003 study. J Clin Oncol 26(15S):4508
24. Garnier C, Rebischung C, Chirpaz E et al (2001) Phase II study of a combination with leucovorin (LV), 5 FU bolus and infusion (FU), gemcitabine (GEM) and oxaliplatin (LOHP) (FOLFU GEMOX regimen) in locally advanced (LA) and metastatic (M) pancreatic carcinoma (APC). Proc Am Soc Clin Oncol 20:620
25. Conroy T, Paillot B, Francois E et al (2005) Irinotecan plus oxaliplatin and leucovorin-modulated fluorouracil in advanced pancreatic cancer—a Groupe Tumeurs Digestives of the Federation Nationale des Centres de Lutte Contre le Cancer study. J Clin Oncol 23(6):1228–1236
26. Ychou M, Desserigne F, Guimbaud R et al (2007) Randomized phase II trial comparing folfirinox (5FU/leucovorin [LV], irinotecan [I] and oxaliplatin [O]) vs gemcitabine (G) as first-line treatment for metastatic pancreatic adenocarcinoma (MPA). First results of the ACCORD 11 trial. J Clin Oncol 25(18S):4516
27. Verslype C, Van Cutsem E, Dicato M et al (2006) The management of pancreatic cancer. Current expert opinion and recommendations derived from the 8th World Congress on Gastrointestinal Cancer, Barcelona, 2006. Ann Oncol 18(7S):vii1–10
28. Huguet F, Andre T, Hammel P et al (2007) Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies. J Clin Oncol 25(3):326–331
29. Rana V, Krishnan S, Abbruzzese JL et al (2006) Neoadjuvant chemotherapy improves outcomes of chemoradiation therapy for locally advanced pancreatic cancer. J Clin Oncol 24(18S):4036
30. Chen LT, Ch'ang HJ, Huang CL et al (2008) Safety-profile of gemcitabine-based chemoradiotherapy (CRT) after triplet induction chemotherapy (CT) in locally advanced pancreatic cancer (LAPC): preliminary data from Taiwan Cooperative Oncology Group (TCOG) T1204 study. In: ASCO Gastrointestinal Cancers Symposium, Orlando; abstract 156