Cancer Chemother Pharmacol (2011) 67:519–525
DOI 10.1007/s00280-010-1351-8

ORIGINAL ARTICLE

Fixed-dose-rate gemcitabine combined with cisplatin in patients with inoperable biliary tract carcinomas

David Goldstein · M. Corona Gainford · Chris Brown · Niall Tebbutt · Stephen P. Ackland · Guy van Hazel · Michael Jefford · Ehtesham Abdi · Sid Selva-Nayagam · Val Gebski · Danielle Miller · Jenny Shannon

Received: 18 March 2010 / Accepted: 27 April 2010 / Published online: 12 May 2010

Abstract
Background Biliary tract cancers (BTC) have a poor prognosis, and there is no consensus on the best chemotherapy regimen. This study determined the response rate for fixed-dose-rate (FDR) gemcitabine combined with cisplatin.
Methods This multicentre phase II trial enrolled 50 patients with inoperable locally advanced or metastatic BTC. Treatment consisted of FDR gemcitabine 1,000 mg/m^2 (10 mg/m^2/min) and cisplatin 20 mg/m^2 on days 1 and 8 of a 21-day cycle. The primary endpoint was response rate. Secondary endpoints included safety, response duration (RD), progression-free (PFS) and overall survival (OS), and cancer antigen 19-9 response.
Results Thirteen patients (26%, 95% CI 14.6–40.4) had a partial response, and 12 (24%) had stable disease. The median RD was 8.3 months (95% CI 6.91–9.99); median PFS 4 months (95% CI 2.5–6.77); and median OS 6.8 months (95% CI 5.0–8.7). Treatment was well tolerated.

For the Australasian Gastrointestinal Trials Group.

Trial registration: ACTRN12605000001695.

D. Goldstein (✉)
Department of Medical Oncology, Prince of Wales Hospital, Barker Street, Randwick, NSW 2031, Australia
e-mail: d.goldstein@unsw.edu.au

M. C. Gainford · C. Brown · V. Gebski · D. Miller
NHMRC Clinical Trials Centre, University of Sydney, Sydney, NSW, Australia

N. Tebbutt
Austin Health, Melbourne, VIC, Australia

S. P. Ackland
Department of Medical Oncology, Calvary Mater Newcastle Hospital, Hunter Medical Research Institute Cancer Research Program, Newcastle, NSW, Australia

G. van Hazel
Department of Medical Oncology, Sir Charles Gairdner Hospital, Perth, WA, Australia

M. Jefford
Division of Haematology and Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

M. Jefford
Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Melbourne, VIC, Australia

E. Abdi
Tweed Cancer Care Centre, Tweed Heads, NSW, Australia

S. Selva-Nayagam
Department of Medical Oncology, Royal Adelaide Hospital, Adelaide, SA, Australia

J. Shannon
Sydney West Cancer Network, Nepean Cancer Care Centre, Sydney, NSW, Australia

Grade 3 and grade 4 nausea, vomiting, and fatigue were uncommon. Thirty-eight per cent of patients discontinued treatment because of toxicity, patient or clinician preference.

Conclusions This treatment combination had moderate activity with acceptable toxicity, supporting previous results that this combination has a role to play. The study does not suggest that FDR gemcitabine is superior to bolus infusion.

Keywords Biliary tract cancer · Cancer antigen 19-9 · Cisplatin · Fixed-dose-rate gemcitabine · Phase II trial

Introduction

Biliary tract carcinomas (BTC) account for 4% of all gastrointestinal neoplasms [1]. Most patients have advanced disease at diagnosis and have an extremely poor prognosis: median survival is generally less than 6 months, and estimated 1- and 2-year survival rates are 25 and 13%, respectively [2]. Complete surgical resection offers the only chance of cure, but only 10% of patients present with operable disease. The goal of treatment for most patients is to reduce symptoms, improve quality of life, and to potentially extend survival. There are differences with respect to disease course and responsiveness to chemotherapy, according to whether the primary site is biliary tree or gallbladder. Traditionally, these entities have been included together in clinical trials, but it has been suggested that they should be segregated in future clinical trials [3].

Owing to the limited number of randomised phase III studies, there is no universally agreed standard chemotherapy regimen. Gemcitabine seems to be one of the most promising. Response rates of 8–36% have been reported for single-agent gemcitabine infused over 30 min, 10–36% for gemcitabine–5 fluorouracil (5FU) combinations, and 27–64% for gemcitabine–cisplatin combinations [4].

The pharmacokinetics of gemcitabine can be optimised by administering it at a fixed-dose rate (FDR) of 10 mg/m^2/min, which allows maximal intracellular accumulation of the active triphosphate form of the drug [5]. One randomised phase II study suggested that gemcitabine monotherapy administered this way may be superior to standard-infusion gemcitabine in patients with advanced pancreatic cancer [6] though a subsequent phase III study did not show a survival benefit [7]. It is uncertain whether FDR gemcitabine might be preferable to bolus gemcitabine for patients with advanced BTC.

The addition of a platinum agent to gemcitabine may confer additional benefit, given that the two agents are synergistic [8, 9]. This finding has recently been substantiated in biliary tract cancers in the preliminary report of a phase III study [10]. The safety and possible improved efficacy of combining FDR gemcitabine was tested in a recent phase II study of gemcitabine 1,000 mg/m^2 at 10 mg/m^2, with cisplatin 20 mg/m^2 on days 1 and 8 of a 21-day cycle. The study reported a response rate of 19% and median time to progression of 3.9 months in 51 patients with metastatic pancreatic adenocarcinoma. The most frequent grade 3 or 4 events were neutropenia and thrombocytopenia [11].

The aims of this study were to determine the objective response rate and to evaluate the toxicities of FDR gemcitabine when used in combination with cisplatin for patients with advanced BTC not amenable to curative resection.

Materials and methods

The protocol conformed to the provisions of the Declaration of Helsinki. Ethics approval was obtained before commencement. All patients gave written informed consent. The trial was conducted by the NHMRC Clinical Trials Centre as an investigator-initiated trial and was registered with the Australian Clinical Trials Trial registry, number 12605000001695.

Eligibility criteria

Eligible patients had histologically or cytologically proven locally advanced unresectable or metastatic BTC with measurable disease. They were ≥18 years of age, had ECOG performance status 0–2, an estimated life expectancy of at least 12 weeks, adequate bone marrow (absolute neutrophil count (ANC) ≥ 1.5×10^9/L, platelet count ≥ 100×10^9/L, haemoglobin ≥ 9 g/dL), and normal liver (aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 5 × upper limit of normal (ULN); bilirubin < 2 × ULN) and renal function (creatinine < 1.5 × ULN and creatinine clearance ≥ 50 mL/min). Patients could not have had chemotherapy for advanced disease or radiotherapy within 4 weeks of commencing the study.

Study design and treatments

This was a multicentre, single-arm phase II study. Treatment consisted of FDR gemcitabine infused at 10 mg/m^2/min (total dose 1,000 mg/m^2), followed by cisplatin 20 mg/m^2 over 1–2 h on days 1 and 8 of each 21-day cycle. Treatment continued until disease progression or unacceptable toxicity. Dose modifications could be made either on days 1 or 8 of a cycle of treatment and were based on the worst toxicity in the preceding cycle. On day 1, gemcitabine was reduced by 25% for ANC < 0.5×10^9/L, platelets < 50 with associated haemorrhage, or platelets < 25. Cisplatin was reduced by 25% if a patient had had grade 2

neuropathy. On day 8, gemcitabine was reduced by 25% if platelets were 50–75 or ANC 0.75–0.99. Both gemcitabine and cisplatin were omitted for platelets < 50 or ANC < 0.75. Gemcitabine was reduced by 25% if serum bilirubin was 2–3 × ULN and omitted if bilirubin was > 3 × ULN or AST or ALT > 5 × ULN.

Assessments and efficacy criteria

Within 4 weeks before enrolment, all patients had baseline radiological imaging with CT or MRI scan. Repeat imaging was performed after every 2 cycles (6 weeks). Standard RECIST (V1.0) criteria of response were used [12]. All responses were confirmed within 4 weeks. The minimal interval required for stable disease was 12 weeks. CA 19-9 response was evaluated as a secondary endpoint and was defined on the basis of the Rustin criteria for CA 125 response in ovarian cancer [13].

Statistical analysis

The primary endpoint was objective tumour response, defined as the total number of complete and partial responses among all enrolled patients; secondary endpoints included duration of response, time to progression, marker response, and overall survival.

This study planned to enrol a minimum of 45 patients using a two-stage minimax design. The sample size calculations were based on the assumption that an objective tumour response rate of 35% or higher was considered sufficient to warrant further evaluation and a rate of 15% or less insufficient. The error rates were set at $\alpha = 0.05$ and $\beta = 0.1$. Enrolment continued to 50 patients to ensure sufficient eligible patients had completed at least one cycle of therapy Criteria were set for early stopping in the event of unexpected severe toxicity or response rates lower or higher than expected. Safety and response data were reviewed by the Trial Management Committee after 16 patients had been recruited.

All eligible patients enrolled in the study were included in the efficacy analysis. All patients who received any treatment were included in the safety analysis. Time to progression, overall survival, and other time-to-event curves were estimated using the Kaplan–Meier method. Tabular data were analysed by chi-squared or exact tests as appropriate.

Results

Demographic data

Fifty patients were enrolled from 13 sites in Australia and New Zealand between February 2005 and October 2006, and all met the eligibility criteria. Demographic and baseline characteristics are listed in Table 1. The median age was 59 (range 39–78). Eighty-eight per cent had performance status ≤1. Twenty-two patients had primary gallbladder cancer and 28 cholangiocarcinoma. Thirty-two had metastatic disease at time of enrolment, with the liver being the most commonly involved site. All patients were followed for at least 18 months.

Table 1 Demographic characteristics of participants of the ABC trial

Characteristic	
Sex (*n*, %)	
Men	23 (46)
Women	27 (54)
Age (*n*, %)	
≤65	37 (74)
>65–75	9 (18)
>75	4 (8)
Average age (years)	
Mean	60.2
Median	58.7
ECOG performance status (*n*,%)	
0	21 (42)
1	23 (46)
2	6 (12)
Primary site at diagnosis (*n*, %)	
Gallbladder	22 (44)
Intrahepatic or extrahepatic bile ducts	25 (50)
Papilla of Vater	2 (4)
Unknown	1 (2)
Extent of disease at baseline (*n*, %)	
Local	34 (68)
Regional lymph node	27 (54)
Distant metastases	32 (64)
Liver involvement	38 (76)
Prior intervention	
Biliary bypass	3 (6)
Biliary stent	15 (30)
Percutaneous biliary drain	2 (4)

Treatment outcome

A median of five cycles of chemotherapy were administered (range 1–21). The most frequent reasons for discontinuing treatment were tumour progression (42%), toxicity (16%), death (16%), patient preference (14%), and clinician preference (8%). Of the initial planned dosages of gemcitabine and cisplatin, administered dose intensities were 93 and 99%, respectively.

In the intention-to-treat population ($n = 50$), 13 patients (26%, 95% CI 14.6–40.4) had a confirmed partial response

by RECIST criteria. Of these, five had primary gallbladder cancer and eight had primary cholangiocarcinoma. Twelve (24%) had stable disease, giving a clinical benefit rate (combined complete response, partial response and stable disease) of 50%. Twenty-two (44%) had progressive disease, and three did not have follow-up assessments. The median response duration was 8.3 months (95% CI 6.9–10.0), and response duration was over 12 months for three of the 13 responders.

The median time to progression was 4 months (95% CI 2.5–6.8) and median overall survival 6.8 months (95% CI 5.0–8.7) (Fig. 1). Fifteen patients survived for over 12 months. Exploratory analysis confirmed that most of these long-term survivors were women (73%), and all had PS $\leq$ 1. In the whole cohort, ECOG performance status was associated with an increased risk of death (1 vs. 0: HR 1.44, 95% CI 0.78–2.68; 2 vs. 0: HR 17.91, 95% CI 5.62–57.11; $P < 0.001$) as were CA 19-9 values (100–1,000: HR 1.92, 95% CI 0.9–3.92; >1,000 vs. <100: HR 2.16, 95% CI 1.06–4.39, $P = 0.06$).

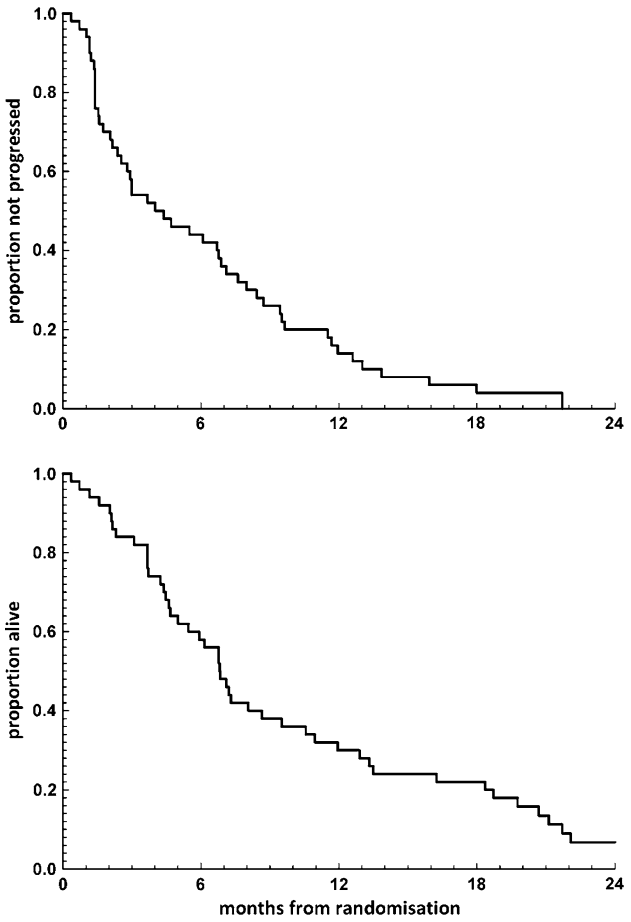

Fig. 1 Progression-free survival for patients in the ABC trial (*upper panel*). Overall survival for patients in the ABC trial (*lower panel*)

Table 2 Types and grades of adverse events in the ABC trial

Toxicity type	Grade (*n*, %)			
	2	3	4	5
Non-haematological				
Infection, with normal neutrophils	8 (16)	9 (18)	0	
Infection, with neutropenia	2 (4)	1 (2)	1 (2)	
Febrile neutropenia	0	4 (8)	0	
Anorexia	14 (28)	2 (4)	0	
Nausea	13 (26)	3 (6)	0	
Vomiting	5 (10)	4 (8)	0	
Diarrhoea	8 (16)	1 (2)	0	
Stomatitis	2 (4)	0	0	
Fatigue	21 (42)	7 (14)	1 (2)	
Haemorrhage				1 (2)[a]
Cardiac infarction				1 (2)[b]
Haematological				
Anaemia	23 (46)	8 (16)	2 (4)	
Neutropenia	9 (18)	13 (26)	7 (14)	
Thrombocytopenia	6 (12)	6 (12)	6 (12)	

[a] Fatal gastrointestinal bleeding (with haematemesis) which was treatment related

[b] Patient had significant cardiac history. Died from non-treatment-related myocardial infarction

Adverse events

Treatment was well tolerated. Grade 3 and grade 4 non-haematological adverse events were minimal (Table 2). Significant nausea, vomiting, and fatigue were uncommon. There was one treatment-related death: haematemesis associated with grade 4 thrombocytopenia. There was no relationship between baseline age and the risk of toxicity or the grade of toxicity.

Response in relation to CA 19-9

Only 9 of the 50 patients had two pre-treatment samples taken, so analysis of CA 19-9 response by the strict Rustin criteria was not meaningful. Exploratory analysis of all patients showed that 17 (34%) had a 50% reduction in their level of CA 19-9. Of these, 7 were confirmed at least 42 days after the first reduced reading. Survival was prolonged in those patients whose CA 19-9 decreased (HR 0.33, $P = 0.054$) but did not reach statistical significance. The median duration of CA 19-9 response was 6.5 months (range 2.1–15.1 months). CA 19-9 reduction showed some association with RECIST ($P = 0.08$). Forty-one per cent of the patients whose CA 19-9 decreased by 50% (and 18% of those who did not) also had a confirmed response by RECIST criteria (Table 3).

Table 3 Association between RECIST and CA19-9 response

CA19-9 reduced from baseline	RECIST response confirmed	
	No	Yes
	Number	Number
Not reduced (≥50%)	27 (82)	6 (18)
Reduced ≥50%	10 (59)	7 (42%)

Discussion

In this study, the confirmed response rate in 50 patients was 26%. The regimen was well tolerated in spite of the significant proportion of relatively older patients in this group.

A pooled analysis of 104 trials involving 2,810 patients with advanced BTC reported a response rate of 22.6% using a variety of chemotherapy regimens [3]. The best response and tumour control rates were seen with gemcitabine and

Table 4 Previous studies of biliary tract cancer

Study	Regimen	Patients	Results
Cholangiocarcinoma and gallbladder			
Valle [10]	Gemcitabine 1,000 mg/m^2 Cisplatin 25 mg/m^2 Days 1 and 8	206 Gallbladder 36% Bile duct 59%	PFS 8.5 months OS 11.7 months
Meyerhardt [14]	Gemcitabine 1,000 mg/m^2 Cisplatin 30 mg/m^2 Days 1 and 8	33 Gallbladder 15% Biliary tract 84%	RR 21% PFS 6.3 months OS 9.7 months
Lee [15]	Gemcitabine 1,250 mg/m^2 Cisplatin 70 mg/m^2 Days 1 and 8	39 Gallbladder 40% Biliary tract 56%	RR 17.1% PFS 3.2 months OS 8.6 months
Giuliani [16]	Gemcitabine 1,000 mg/m^2 Days 1 and 8 Cisplatin 75–80 mg/m^2 Day 1 only	38 Gallbladder 26% Biliary tract 74%	RR 32% PFS 4 months OS 8 months
Park [17]	Gemcitabine 1,000 mg/m^2 Days 1, 8 and 15 Cisplatin 75 mg/m^2 Day 1 only	27 Gallbladder 48% Biliary tract 53%	RR 33.3% PFS 5.6 months OS 10.0 months
Kim [18]	Gemcitabine 1,250 mg/m^2 Days 1 and 8 Cisplatin 60mg/m^2 Day 1 only	29 Gallbladder 34% Biliary tract 62%	RR 34.5% FRS 3.0 months OS 11 months
Thongprasert [19]	Gemcitabine 1250 mg/m^2 Days 1 and 8 Cisplatin 75 mg/m^2 Day 1 only	43 Gallbladder 2% Biliary tract 88%	RR 27.5% PFS 21 weeks OS 36 weeks
Goldstein	Fixed-dose-rate gemcitabine at 10 mg/m^2/min (total dose 1,000 mg/m^2) Cisplatin 20 mg/m^2 Days 1 and 8	50 Gallbladder 44% Biliary 50%	RR 26% PFS 4 months OS 6.8 months
Primary gallbladder			
Doval [20]	Gemcitabine 1,000 mg/m^2 Days 1 and 8 Cisplatin 70 mg/m^2 Day 1 only	30	RR 36.6% PFS 18 weeks OS 20 weeks
Reyes-Vidal [21]	Gemcitabine 1,250 mg/m^2 Cisplatin 35 mg/m^2 Days 1 and 8	44	RR 47.5%
Primary biliary tract			
Lee [22]	Gemcitabine 1,000 mg/m^2 Days 1 and 8 Cisplatin 70 mg/m^2 Day 1 only	24	RR 20.8% OS 9.3 months

platinum combinations. The recent phase III study confirmed the superior efficacy of gemcitabine combined with cisplatin compared with gemcitabine alone [10]. The median OS was greater with the combination treatment than gemcitabine alone; 11.7 versus 8.2 months ($P = 0.002$) amongst 324 patients stimulating interest in obtaining optimal outcomes with the gemcitabine and cisplatin combination.

Our results are consistent with this result and the more recent phase II studies that used this combination. Using a range of chemotherapy doses and schedules (Table 4), studies of a mixture of gallbladder carcinomas and cholangiocarcinomas have reported response rates of 17–34.5% [10, 14–19]. In studies of primary gallbladder cancer only, response rates have been higher. Doval reported a response rate of 37% [20], and Reyes Vidal a response rate of 47.5% [21]. One study of cholangiocarcinoma reported a response rate of 21% [22].

All of these studies used bolus-infusion gemcitabine. Our study is the only one to use the FDR infusion scheduling in combination therapy, but it does not suggest that this regimen enhances the benefit of treatment. Indeed, the slightly lower than average progression-free survival may suggest that it is not the optimal schedule of gemcitabine to use in this setting. Among the reported studies, ours also used the lowest dose of cisplatin. Given the acceptable activity and toxicity profile reported here, this suggests that higher doses of cisplatin may not be necessary for a meaningful response rate.

Serially measured CA 19-9 levels have been shown to correlate with clinical outcomes, and CA 19-19 is an independent prognostic factor for survival in patients with pancreatic cancer [23]. A study in patients with biliary tract cancers suggested that pre-treatment CA 19-9 and decrease in CA 19-9 after chemotherapy are of prognostic relevance [24]. Patients with locally advanced or metastatic biliary tract carcinoma often do not have readily measurable disease. Therefore, using CA 19-9 as an alternative to RECIST to identify patients who should continue with treatment is an important goal. Our study, even with small numbers, suggests associations between a reduction in CA 19-9 and RECIST response and between a reduction in CA 19-9 and survival. CA 19-9 was not as strong a predictor of overall survival as RECIST. Common complications in patients with biliary tract cancers are stent occlusion and cholangitis, which result in non-cancer-related increase in CA 19-9 levels; this should be accounted for in future studies.

Since this study was designed, newer chemotherapeutic combinations have been tested, and response rates of 17–32% have been reported for gemcitabine and capecitabine [25, 26], 22–50% for gemcitabine and oxaliplatin [27, 28], and 40% for epirubicin, cisplatin, and capecitabine [29] in patients with advanced BTC. These results provide encouragement for further studies to investigate the effect of novel chemotherapy combinations in addition to those combining targeted agents, with a standard of gemcitabine and cisplatin.

In summary, we have shown that the combination of FDR gemcitabine with cisplatin has moderate activity with acceptable toxicity for patients with advanced BTC. It was well tolerated, and responses were durable in 30% of the responders. It supports the results of previous studies that this combination has a role to play in the effective palliation of BTC. When compared with similar studies using bolus gemcitabine, the study does not suggest that FDR gemcitabine is clearly superior to bolus infusion. For the present, we suggest that bolus gemcitabine is the appropriate backbone for subsequent studies adding new targeted therapies to advance research in this disease.

Acknowledgments Numerous individuals from many institutions participated to complete this study. The authors thank everyone involved for their efforts. This work was supported by an unrestricted educational grant from Eli Lilly, a Partnership grant from the Cancer Institute NSW, and by the National Health and Medical Research Council Clinical Trials Centre.

Conflict of interest statement The authors have no conflict of interest to declare.

References

1. Greenlee RT, Hill-Harmon MB, Murray T et al (2001) Cancer statistics, 2001. CA Cancer J Clin 51:15–36
2. Patel T (2002) Worldwide trends in mortality from biliary tract malignancies. BMC Cancer 2:10
3. Eckel F, Schmid RM (2007) Chemotherapy in advanced biliary tract carcinoma: a pooled analysis of clinical trials. Br J Cancer 96:896–902
4. Pasetto LM, D'Andrea MR, Falci C et al (2007) Gemcitabine in advanced biliary tract cancers. Crit Rev Oncol Haematol 61:230–242
5. Abbruzzese JL, Grunewald R, Weeks EA et al (1991) A phase I clinical, plasma and pharmacology study of gemcitabine. J Clin Oncol 9:491–498
6. Tempero M, Plunkett W, van Haperen VR et al (2003) Randomised phase II comparison of fixed dose-intense gemcitabine: thirty minute infusion and fixed dose rate infusion in patients with pancreatic adenocarcinoma. J Clin Oncol 21:3402–3408
7. Poplin E, Feng Y, Berlin J et al (2009) Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the eastern cooperative oncology. J Clin Oncol 27:3778–3785
8. Peters GJ, Bergman AM, Ruiz van Haperen VW et al (1995) Interaction between cisplatin and gemcitabine in vitro and in vivo. Semin Oncol 22:72–79
9. Van Moorsel CJ, Pinedo HM, Veerman G et al (1999) Mechanisms of synergism between cisplatin and gemcitabine in ovarian and non-small cell lung cancer cell lines. Br J Cancer 80:981–990
10. Valle JW, Wasan HS, Palmer DD et al (2009) Gemcitabine with or without cisplatin in patients with advanced or metastatic biliary

tract cancer: results of a multicenter, randomized phase III trial (the UK ABC-02 trial). J Clin Oncol 27:15s (abstract 4503)
11. Ko A, Dito E, Schillinger B et al (2006) Phase II study of fixed dose rate gemcitabine with cisplatin for metastatic adenocarcinoma of the pancreas. J Clin Oncol 24:379–385
12. Therasse P, Arbuck SG, Eisenhauer EA et al (2000) New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 92:205–216
13. Rustin GJ, Nelstrop AE, McClean P et al (1996) Defining response of ovarian carcinoma to initial chemotherapy according to serum CA 125. J Clin Oncol 14:1545–1551
14. Meyerhardt JA, Zhu A, Stuart K et al (2008) Phase II study of gemcitabine and cisplatin in patients with metastatic biliary and gallbladder cancer. Dig Dis Sci 53:564–570
15. Lee J, Kim TY, Lee MA et al (2008) Phase II trial of gemcitabine combined with cisplatin in patients with inoperable biliary tract carcinomas. Cancer Chemother Pharmacol 61:47–52
16. Giuliani F, Gebbia V, Maiello E et al (2006) Gemcitabine and cisplatin for inoperable and/or metastatic biliary tree carcinomas: a multicentre phase II study of the Gruppo Oncologica dell'Italia Meridionale. Ann Oncol 17:vii73–vii77
17. Park BK, Kim YJ, Park JY et al (2006) Phase II study of gemcitabine and cisplatin in advanced biliary tract cancer. J Gastronenterol Hepatol 21:993–1003
18. Kim ST, Park JO, Lee J et al (2006) A phase II study of gemcitabine and cisplatin in advanced biliary tract cancer. Cancer 106:1339–1346
19. Thongprasert S, Napapan S, Charoentum C et al (2005) Phase II study of gemcitabine and cisplatin as first line chemotherapy in inoperable biliary tract carcinoma. Ann Oncol 16:279–281
20. Doval DC, Sekhon JS, Gupta SK et al (2004) A phase II study of gemcitabine and cisplatin in chemotherapy naïve, unresectable gallbladder cancer. Br J Cancer 90:1516–1520
21. Reyes-Vidal J, Gallardo J, Yanez E et al (2003) Gemcitabine and cisplatin in the treatment of patients with unresectable or metastatic gallbladder cancer: results of the phase II GOCCHI study. Proc Am Soc Clin 22:273 abstract 1095
22. Lee GW, Kang JH, Kim HG et al (2006) Combination chemotherapy with gemcitabine and cisplatin as first line treatment for immunohistochemically proven cholangiocarcinoma. Am J Clin Oncol 29:127–131
23. Ko AH, Hwang J, Venook AP et al (2005) Serum CA19–9 response as a surrogate for clinical outcome in patients receiving fixed dose rate gemcitabine for advanced pancreatic cancer. Br J Cancer 93:195–199
24. Harder J, Kummer O, Olschewski M et al (2007) Prognostic relevance of Carbohydrate Antigen 19.9 levels in patients with advanced biliary tract cancer. Cancer Epidemiol Biomarkers Prev 16:2097–2100
25. Riechelmann RP, Townsley CA, Chin SN et al (2007) Expanded phase II trial of gemcitabine and capecitabine for advanced biliary cancer. Cancer 110:1307–1312
26. Iyer RV, Gibbs J, Kuvshinoff B et al (2007) A phase II study of gemcitabine and capecitabine in advanced cholangiocarcinoma and carcinoma of the gallbladder. A single institution study. Ann Surg Oncol 14:3202–3209
27. Andre T, Tournigand C, Rosmorduc O et al (2004) Gemcitabine combined with oxaliplatin in advanced biliary tract adenocarcinoma. A GERCOR study. Ann Oncol 15:1339–1343
28. Verderame F, Russo A, Di Leo R et al (2006) Gemcitabine and oxaliplatin combination chemotherapy in advanced biliary tract cancers. Ann Oncol 17(suppl 7):68–72
29. Park SH, Park YH, Lee JN et al (2006) Phase II study of epirubicin, cisplatin and capecitabine for advanced biliary tract adenocarcinoma. Cancer 106:361–365