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REVIEW

Options for the Treatment of Gemcitabine-Resistant Advanced Pancreatic Cancer

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Summary

Context Pancreatic cancer is noteworthy in that the number of patients dying from the disease is roughly equal to the number diagnosed. For more than a decade, gemcitabine has constituted the standard of care for the palliative treatment of the majority of patients who present with metastatic or relapsed disease, although the survival gains are limited. Despite a median survival of less than 6 months, there is a significant proportion of advanced pancreatic cancer patients who progress on gemcitabine that remains fit and these patients are candidates for second-line treatment. **Methods** The OVID MEDLINE database was searched from 1950 to present using the MeSH terms "pancreatic neoplasms", "drug treatment" and "gemcitabine". After excluding non-relevant results, 31 published studies were identified. These results were supplemented by searching the last three (2007-2009) American Society of Clinical Oncology (ASCO) Proceedings of Annual Meetings for studies published only in abstract form and reviewing reference lists of published articles. **Results and discussion** The evidence for second line treatments of metastatic pancreatic cancer consists mostly of single arm, small phase II studies. Oxaliplatin-fluoropyrimidine combinations appear promising and have shown increased survival compared to best supportive care. As the molecular pathways governing pancreatic cancer are unravelled, novel targeted therapies may offer the greatest promise for this disease either given alone, combined with one another, or with cytotoxic agents. The need for further, collaborative research is emphasised.

Introduction

According to Surveillance Epidemiology and End Results (SEER) estimates, more than 42,000 patients will be diagnosed with pancreatic cancer in the United States in 2009 [1]. With 35,000 deaths attributed to the disease over the same time period, pancreatic cancer constitutes the 4th most common cause of death from malignancy. The situation is similar in Europe, where just over 60,000 patients were diagnosed with pancreatic cancer in 2006 and almost the same number died from their disease [2]. More than 80% of patients present with unresectable, locally advanced or metastatic disease, the prognosis of which remains dismal with a median survival of approximately 6 months and fewer than 2% of patients surviving for 5 years [1].

Gemcitabine has been the standard of care for the first line treatment of metastatic pancreatic cancer since 1997, when it was shown to improve survival compared to 5-fluorouracil (5-FU). In the pivotal trial reported by Burris *et al.*, treatment with gemcitabine resulted in a median survival of 5.65 months compared to 4.41 months with bolus 5-FU, together with an improvement in clinical benefit response of 23.8% compared with 4.8%. More impressively, 1-year survival increased from 2% to 18%, establishing gemcitabine as the preferred initial treatment option [3]. Over the past decade multiple phase II and III studies have attempted to improve on the above results with various combinations of gemcitabine with traditional cytotoxic or novel targeted agents. A phase III trial has shown a modest improvement in overall survival with the addition of erlotinib [4] to standard gemcitabine chemotherapy, whereas the initially

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Abbreviation ASCO: American Society of Clinical Oncology; COX-2: cyclo-oxygenase 2; EGFR: epidermal growth factor receptor; FAM: 5-fluorouracil, doxorubicin, mitomycin-C; FF: folinic acid, 5-fluorouracil; FOLFIRI.3: irinotecan, folinic acid, infusional 5-fluorouracil; FOLFOX: oxaliplatin, folinic acid, infusional 5-fluorouracil; GEMOX: gemcitabine, oxaliplatin; G-FLIP: gemcitabine, irinotecan, folinic acid, 5-fluorouracil, cisplatin; IROX: irinotecan, oxaliplatin; KRAS: v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; mTOR: mammalian target of rapamycin; NCCN: National Comprehensive Cancer Centre; OFF: oxaliplatin, folinic acid, 5-fluorouracil; OS: overall survival; PDGFR: platelet-derived growth factor receptor; PEFG: cisplatin, 5-fluorouracil, epirubicin, gemcitabine; PFS: progression-free survival; PS: performance status; TKI: tyrosine kinase inhibitor; TTP: time to progression; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor; XELOX: oxaliplatin, capecitabine

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reported survival advantage from the addition of capecitabine [5], was no longer evident with more complete follow up [6]. A third study has reported improved progression-free survival with the addition of bevacizumab to a combination of gemcitabine and erlotinib [7]. However, currently, there remains a lack of convincing evidence that any single or combination drug regimen yields consistent, clinically meaningful, survival benefits compared with single agent gemcitabine.

While the standard of care in the first line setting is established, there is limited data available to guide treatment decisions in patients whose disease has progressed following gemcitabine treatment. This is exemplified by the National Comprehensive Cancer Centre (NCCN) pancreatic cancer guidelines that suggest participation in a clinical trial as the preferred treatment option for patients who have previously received gemcitabine [8]. Given the short life expectancy with advanced pancreatic cancer, many patients deteriorate quickly after disease progression, rendering further active treatment inappropriate. However, perhaps as many as 1 in 3 patients are fit enough for consideration of a second line option. Generally, this group includes patients with good performance status (WHO 0-1) and adequate haematological, renal and hepatic function who wish to proceed with treatment after an informed discussion regarding the potential benefits of such an option. The earlier detection of disease progression or relapse with the use of advanced imaging technologies and serum tumour markers is likely to expand the pool of suitable patients.

In this review article, we present an overview of the available published data on second line therapy for advanced disease. In order to identify relevant studies, the OVID Medline database was searched from 1950 to present using the MeSH terms “pancreatic neoplasms”, “drug treatment” and “gemcitabine”. After excluding non-relevant results, 31 published studies were identified. These results were supplemented by searching the last 3 (2007-2009)

Table 1. Prospective single arm phase II chemotherapy trials in gemcitabine-resistant metastatic pancreatic cancer.

Study	Regimen	No. of patients	Partial response + complete response (PR+CR: %)	Median progression-free survival (PFS: months)	Median overall survival (OS: months)
Pelzer *et al*. [9]	OFF	37	6	2.8	5.1
Tsavaris *et al*. [12]	OFF	30	23	n/a	5.8
Novarino *et al*. [13]	OFF	23	0	2.7	4.0
Xiong *et al*. [16]	XELOX	41	2	2.3	5.3
Gasent Blesa *et al*. [17]	XELOX	15	7	n/a	5.3
Sancho *et al*. [18]	XELOX	18	5	4.0	5.8
Androulakis *et al*. [19]	Oxaliplatin	18	0	n/a	n/a
Demols *et al*. [21]	GEMOX	33	21	4.2	6.0
Mazzer *et al*. [25]	Oxaliplatin, pemetrexed	16	19	3.2	n/a
Reni *et al*. [26]	Oxaliplatin, raltitrexed	41	24	n/a	5.2
Cantore *et al*. [24]	IROX	30	10	4.1	5.9
Morizane *et al*. [27]	S-1	40	15	2.0	4.5
Boeck *et al*. [29]	Capecitabine	39	0	2.3	7.6
Togawa *et al*. [30]	Cisplatin, S-1	17	29	n/a	9.0
Kim *et al*. [33]	5-FU, paclitaxel	28	7	2.5	7.6
Lee *et al*. [34]	FAM	15	0	2.3	6.7
Blaya *et al*. [35]	Capecitabine, docetaxel	24	12.5	n/a	n/a
Pino *et al*. [38]	Capecitabine, celecoxib	35	9	n/a	4.4
Millela *et al*. [37]	5-FU, celecoxib	17	12	1.9	3.5
Saif *et al*. [39]	Capecitabine, PHY906	25	4	n/a	n/a
Yi *et al*. [40]	Irinotecan	33	9	2.0	6.0
Ko *et al*. [41]	Docetaxel, irinotecan	14	0	1.2	4.4
Reni *et al*. [42]	Mitomycin C, docetaxel, irinotecan	15	0	1.7	6.1
Burris *et al*. [44]	Rubitecan	58	5	1.9	3.0
Cereda *et al*. [46]	Docetaxel	10	0	1.5	4.0
Carvajal *et al*. [47]	Docetaxel, flavopiridol	10	0	n/a	n/a
Oettle *et al*. [48]	Paclitaxel	18	6	n/a	4.1
Boeck *et al*. [49]	Pemetrexed	52	4	1.6	4.7
Moore *et al*. [50]	Eribulin	15	0	n/a	n/a
Stathopoulos *et al*. [51]	Lipoplatin, gemcitabine	24	8	3.0	n/a
Tschoep *et al*. [52]	Regional hyperthermia, gemcitabine, cisplatin	22	9	4.2	n/a

FAM: 5-fluorouracil, doxorubicin, mitomycin C; GEMOX: gemcitabine, oxaliplatin; IROX: irinotecan, oxaliplatin; OFF: oxaliplatin, folinic acid, 5-fluorouracil; XELOX: capecitabine, oxaliplatin
n/a: not available

Table 2. Prospective randomised phase II and III trials in gemcitabine-resistant metastatic pancreatic cancer.

Study	Regimen	No. of patients	Partial response + complete response (PR+CR: %)	Median progression-free survival (PFS: months)	Median overall survival (OS: months)
Oettle *et al*. [10]	OFF Best supportive care	46 (total)	n/a	n/a	4.9 2.3 (P=0.008)
Pelzer *et al*. [11]	OFF FF	76 84	n/a	3.0 2.1 (P=0.012)	6.0 3.0 (P=0.014)
Hwang *et al*. [15]	FOLFOX FOLFIRI.3	30 30	n/a	1.4 1.9 (P>0.05)	4.0 4.0 (P>0.05)
Ulrich-Pur *et al*. [43]	Irinotecan, raltitrexed Raltitrexed	19 19	16 0	4.0 2.5	6.5 4.3
Jacobs *et al*. [45]	Rubitecan Best care [a]	198 211	11 1 (P<0.001)	1.9 1.6 (P=0.003)	3.5 3.1 (P=0.626)
Astsaturov *et al*. [64]	Bevacizumab Bevacizumab, docetaxel	15 15	0 7	1.4 1.5 (P=0.5)	5.9 4.0 (P=0.8)

FF: folinic acid, 5-fluorouracil; FOLFIRI.3: irinotecan, folinic acid, infusional 5-fluorouracil; FOLFOX: oxaliplatin, folinic acid, infusional 5-fluorouracil; OFF: oxaliplatin, folinic acid, 5-fluorouracil

[a] clinician's choice of chemotherapy or best supportive care

n/a: not available

American Society of Clinical Oncology (ASCO) Proceedings of Annual Meetings for studies published only in abstract form and reviewing reference lists of published articles. The evidence for second line treatments of metastatic pancreatic cancer consists mostly of single arm, small phase II studies, testing a variety of drug combinations in a heterogeneous population. Therefore, a descriptive approach was adopted, as any attempt at statistical analysis using meta-analytic approaches would be inappropriate.

Oxaliplatin-Fluoropyrimidine Combinations

The combination of oxaliplatin with a fluoropyrimidine appears promising in phase II second line trials and is one of only a handful of regimens evaluated in the phase III setting (Tables 1 and 2). In an initial phase II study, Pelzer *et al*. [9] reported on the efficacy of the OFF (oxaliplatin, folinic acid, 5-FU) regimen, combining oxaliplatin 85 mg/m^2 on days 8 and 22, folinic acid 500 mg/m^2 and 5-FU 2,600 mg/m^2 as a 24-h infusion on days 1, 8, 15 and 22. The regimen was repeated every 42 days and toxicity was apparently quite acceptable, with grade 3 non-haematologic adverse events occurring in 32% of patients and no reported grade 4 non-haematologic toxicities. Thirty seven gemcitabine-pretreated patients were enrolled and the median time to progression (TTP) and overall survival (OS) were 12 and 22 weeks, respectively. Two patients (6%) showed radiological responses, while a further 16 (43%) had stable disease for more than 12 weeks.

These results prompted a phase III study (Charité Onkologie; CONKO 003). The initial study design was a comparison of the OFF regimen (modifying the 5-FU dose to 2,000 mg/m^2 and the folinic acid dose to 200 mg/m^2) with best supportive care. Eligibility criteria included progression on previous gemcitabine-based chemotherapy, adequate haematological, renal, cardiac and hepatic function and a Karnofsky performance status greater than 70. Unfortunately, the control arm was closed after 46 of the planned 165 patients were enrolled due to clinician reluctance to enroll in a no-treatment arm. The results of this initial cohort of the trial were presented at the 2005 ASCO Annual Meeting [10]. Median survival was 22 weeks in the experimental arm and 10 weeks in the best supportive care arm (P=0.0077).

Given this impressive survival difference, the trial design was altered to include an alternative relevant comparator arm, comprising 5-FU plus folinic acid chemotherapy (FF regimen) at the same doses and the trial therefore became a randomised comparison of OFF *versus* FF. A further 165 patients were enrolled and results for the 160 assessable patients were presented at the 2008 ASCO Annual Meeting [11]. Toxicity was acceptable with few grade 3-4 adverse events. Median progression-free survival (PFS) and overall survival were significantly better in the OFF arm (13 *vs*. 9 weeks, P=0.012, and 26 *vs*. 13 weeks, P=0.014, respectively).

Two further single arm phase II studies using oxaliplatin plus bolus 5-FU/folinic acid have been reported. Tsavaris *et al*. [12] administered weekly oxaliplatin (50 mg/m^2), bolus folinic acid (50 mg/m^2) and 5-FU as a 1-h infusion (500 mg/m^2). Thirty gemcitabine-pretreated patients were enrolled, 29 of whom had locally advanced disease. Seven patients showed a partial response and a further 9 had stable disease for a disease control rate (partial response plus stable disease) of 53%. The median duration of response was 22 weeks and median survival was 25 weeks. Of note, 27% of patients experienced febrile neutropenic events but there were no treatment related fatalities.

Novarino *et al*. [13] also utilised a weekly oxaliplatin/5-FU/folinic acid regimen (oxaliplatin 40 mg/m^2, folinic acid 250 mg/m^2, and 5-FU 500 mg/m^2 on a 3 week-on/1 week-off schedule). Twenty three patients were enrolled, 17 were assessable and no objective responses were seen. Four patients had stable disease for a median duration of stable disease of 14 weeks. The median TTP was 11.6 weeks and median survival was 17.1 weeks. Grade 3-4 toxicity occurred in 7 (30%) patients.

Using a combination regimen more familiar to colorectal cancer specialists, FOLFOX4 (oxaliplatin 85 mg/m^2 on day 1, levo-folinic acid 100 mg/m^2 over 2 h, 5-FU 400 mg/m^2 i.v. bolus then 600 mg/m^2 over 22 h on days 1 and 2 every two weeks), Gebbia *et al*. reported a retrospective case series of 42 patients [14]. Six (14%) partial responses and 16 (38%) cases of stable disease were seen. Twenty seven patients reported subjective improvement; the median TTP was 4 months and the median survival was 6.7 months. Although encouraging, these results are subject to the usual limitations of a retrospective design, with unclear selection criteria.

Hwang *et al*. [15] presented the first results of a small randomised phase II trial of the FOLFOX (oxaliplatin, folinic acid, infusional 5-fluorouracil) regimen at the 2009 ASCO Annual Meeting (Table 2). Sixty patients with advanced pancreatic cancer and previous progression on gemcitabine were randomised to modified FOLFOX (oxaliplatin 85 mg/m^2, folinic acid 400 mg/m^2, and 5-FU 2,000 mg/m^2 over 46 hours every two weeks) or FOLFIRI.3 (the same 5-FU/folinic acid regimen but with irinotecan 70 mg/m^2 every two weeks). Thirty patients were enrolled in each arm and median survival was identical at 4 months. The median PFS was 1.4 and 1.9 months for FOLFOX and FOLFIRI.3, respectively (P>0.05); slightly more patients in the latter (28% *vs*. 20%) achieved disease control (defined as partial response or stable disease).

Finally, three small single arm phase II studies have investigated the efficacy of oxaliplatin-capecitabine combinations. Xiong *et al*. [16] enrolled 41 gemcitabine-pretreated patients on a single arm study of XELOX (oxaliplatin and capecitabine) in advanced pancreatic cancer (oxaliplatin 130 mg/m^2, capecitabine 1,000 mg/m^2 *po bid* days 1-14, every 3 weeks). One (2%) patient showed a partial response and a further 10 (24%) had stable disease. The median PFS was 10 weeks and the median survival 23 weeks. Grade 3 or worse non-haematologic toxicities were uncommon with only fatigue and diarrhoea occurring in more than 1 patient. Two more, smaller, studies have been presented in abstract format only. The first, by Gasent-Blesa *et al*. [17] enrolled 15 patients. Treatment was with a modified XELOX regimen in which the oxaliplatin dose was reduced to 100 mg/m^2. One patient had a complete response and a further 5 had stable disease. Median survival from initiation of second-line treatment was 163 days (23 weeks) and the regimen was well tolerated with no grade 3-4 adverse events. Sancho *et al*. [18] also performed a study of XELOX in advanced gemcitabine-resistant pancreatic and biliary adenocarcinoma. Eighteen patients (9 with pancreatic cancer) were enrolled and the median PFS and OS were 17 and 25 weeks respectively. There was no information on the outcomes of the pancreatic cancer patients separately. It should be noted that the toxicity of the full dose XELOX regimen was higher than that reported by Xiong *et al*. and Gasent-Blesa *et al*., with 11 grade 3 adverse events.

In summary, oxaliplatin-fluoropyrimidine combinations appear to show some promising activity in gemcitabine-pretreated patients. The OFF regimen has been shown to be superior to best supportive care or 5-FU/folinic acid in a randomised study and might be considered as an emerging standard of care in this setting. To date, it remains the only regimen that has achieved a survival advantage in a randomised trial, a position recognised by the NCCN guidelines that recommend the use of oxaliplatin and fluoropyrimidine combination if enrolment in a clinical trial is not possible [8]. Although direct comparisons are lacking, the XELOX regimen shows comparable efficacy and offers the advantage of oral fluoropyrimidine treatment, obviating the need for infusion pumps with associated complications and more frequent hospital attendances. Even so, more large scale, well designed, randomised controlled trials are required in this setting before a new standard of care can be established.

Other Oxaliplatin Based Combinations

Studies of oxaliplatin as single agent or in combination with a non-fluoropyrimidine are summarised in Table 1. As might be predicted from both preclinical and clinical studies in colorectal cancer, single agent oxaliplatin (130 mg/m^2 every 3 weeks) was shown to be inactive in a small study involving 18 patients [19]. No responses were seen, with just 3 (17%) patients achieving stable disease for more than 2 months.

Based upon initial data suggesting that fixed-dose-rate gemcitabine (10 mg/m^2/min) results in higher intracellular accumulation of active gemcitabine metabolites and higher response rates (although at the cost of increased toxicity) [20], Demols *et al*. [21] tested the hypothesis that the addition of oxaliplatin to fixed-dose-rate gemcitabine in patients whose disease had previously progressed on standard single agent gemcitabine would restore chemosensitivity. They enrolled 33 patients to a phase II study of GEMOX (gemcitabine 1,000 mg/m^2 over 100 min on day 1, oxaliplatin 100 mg/m^2 on day 2 every 2 weeks). Toxicity was considerable, with one patient fatality from neutropenic sepsis and 48% experiencing at least one grade 3 toxic event. The regimen showed evidence of activity with 7 (21%) of patients showing partial response and a further 11 (33%) stable disease for more than 8 weeks. Median TTP and OS were 4.2 and 6 months respectively. Recently, Fortune *et al*. [22] reported their institutional experience with the

GEMOX regimen, again utilising fixed-dose-rate gemcitabine. Seventeen patients that had progressed on previous gemcitabine treatment were retrospectively identified. There were 4 (24%) partial responses and 5 (29%) cases of stable disease. The median PFS was 2.6 months whereas the median survival was 6.4 months. The toxicity of GEMOX is significant and, in view of the findings of the phase III E6201 study [23] in the first-line setting, further evaluation for the second-line treatment of pancreatic cancer does not appear to be worthwhile. E6201 was a randomised study of gemcitabine *versus* fixed-dose-rate gemcitabine *versus* GEMOX in previously untreated patients with advanced pancreatic cancer. More than 800 patients were enrolled and although toxicity was increased in both experimental arms, no survival or clinical benefit was noted [23].

Oxaliplatin has also been investigated in combination with irinotecan (IROX) with some preliminary evidence of efficacy [24]. Thirty patients were treated with oxaliplatin (60 mg/m^2 days 1 and 15) and irinotecan (60 mg/m^2 days 1, 8 and 15 every 4 weeks); 3 (10%) partial responses were noted and the disease remained stable in a further 7 (23%) patients. The regimen was well tolerated and median TTP and survival were 4.1 and 5.9 months, respectively.

The combination of oxaliplatin (120 mg/m^2) with pemetrexed (500 mg/m^2 every 3 weeks) may have some activity. Initial results of a phase II study presented at the 2009 ASCO Annual Meeting showed 3 partial and 6 minor responses in 15 evaluable patients. The median PFS was 14 weeks and grade 3 toxicities appeared uncommon [25]. Oxaliplatin (130 mg/m^2) has also been combined with another novel antifolate, raltitrexed (3 mg/m^2). Forty one patients were treated in a phase II trial and the partial response rate was an encouraging 24% [26]. Significant toxicity was uncommon, but, disappointingly, median survival was only 5.2 months.

Single-Agent Fluoropyrimidines

Two single arm phase II studies and a retrospective series have addressed the role of a fluoropyrimidine as a single agent following disease progression on gemcitabine. Morizane *et al*. [27] reported on the use of S-1, a novel oral fluoropyrimidine prodrug, in this setting. S-1 consists of ftorafur, a 5-FU prodrug, combined with the dihydropyrimidine dehydrogenase (DPD) inhibitor, chloro-dihydroxypyridine, and the orotate phosphoribosyltransferase inhibitor potassium oxonate. In the study by Morizane *et al*., 40 patients received S-1 at a dose of 40 mg/m^2 daily for 28 days followed by a 14-day rest period. Six (15%) patients had a partial response and 17 (43%) had stable disease. Median PFS and OS were 2 and 4.5 months, respectively. Nakai *et al*. [28] reported their institutional experience with S-1 in the second line treatment of gemcitabine-resistant pancreatic cancer at the University of Tokyo Hospital. Twenty nine patients were treated with 5 (17%) responding. Median PFS and OS were 2.5 and 7.8 months, respectively.

Capecitabine (1,250 mg/m^2 *po bid* for 2 weeks every 3 weeks) was administered to 39 patients by Boeck *et al*. [29]. No objective responses were seen and 13% of patients experienced grade 3 palmar-plantar erythema. Median TTP was 2.3 months and median survival was 7.6 months in this study, indicating some efficacy, even in the absence of objective responses.

Cisplatin-Fluoropyrimidine Combinations

Evidence regarding the use of cisplatin in patients with gemcitabine-resistant disease is limited (Table 1). A small single arm Japanese phase II study tested the combination of cisplatin and S-1 [30]. The regimen consisted of S-1 80 mg/m^2 daily for 21 days, followed by a 14-day rest period, and cisplatin 40 mg/m^2 on day 8. Seventeen patients were enrolled with 5 (29%) showing partial response and a further 2 (12%) stable disease. The median survival was an impressive 9 months and 32% were still alive at 12 months. Treatment was well tolerated with only a single episode of grade 3 toxicity (leukopaenia). However, of note, in this study all patients had received gemcitabine adjuvantly and treatment with cisplatin and S-1 was in the first line metastatic setting, which most probably explains the prolonged median survival compared to other studies in this review.

A four drug combination of cisplatin, 5-FU, epirubicin and gemcitabine (PEFG) was tested by Reni *et al*. [31]. This was an observational study with two cohorts of gemcitabine-resistant patients treated either with "classic" (cisplatin and epirubicin 40 mg/m^2 day 1, gemcitabine 600 mg/m^2 days 1 and 8, 5-FU 200 mg/m^2/day continuous infusion days 1-28) or "dose-intense" PEFG (cisplatin and epirubicin 30 mg/m^2, gemcitabine 800 mg/m^2 every 14 days; 5-FU 200 mg/m^2/day continuous infusion days 1-28). Dose intensification led to more common grade 3 and 4 haematological toxicity but non-haematological toxicity was generally mild with both regimens. There were no significant differences in efficacy between the "classic" and the "dose-intense" cohort. Response rates, median PFS and OS for the 46 enrolled patients were 24%, 5 months and 8.3 months, respectively.

Another intensive regimen incorporating both cisplatin and 5-FU is G-FLIP. The regimen consists of gemcitabine (500 mg/m^2 day 1), irinotecan (80 mg/m^2 day 1), folinic acid (300 mg days 1 and 2), 5-FU (400 mg/m^2 i.v. bolus followed by 600 mg/m^2 over 8 hours days 1 and 2) and cisplatin (50-75 mg/m^2 day 2). In a retrospective series, Kozuch *et al*. [32] reported their experience with 34 gemcitabine-resistant patients. Grade 3-4 haematological toxicities were common and 8 (24%) patients experienced a partial response. The median PFS was 3.9 months, whereas the median survival was an impressive 10.3 months.

These two observational studies appear to show that improved efficacy can be achieved by combining multiple non-crossresistant agents. However, the toxicity of the regimens appears high, potentially limiting their use in a select subset of patients. It remains to be seen whether comparative efficacy is

achieved in prospectively designed, preferably randomised, studies.

Other Fluoropyrimidine-Based Combinations

Studies have also been conducted combining a fluoropyrimidine with a non-platinum agent (Table 1). Kim *et al*. combined 5-FU (1,000 mg/m^2/day on days 1-3) with paclitaxel (175 mg/m^2). Twenty eight patients were enrolled, of which 2 (7%) showed a partial response to treatment. Median TTP and OS were 2.5 and 7.6 months, respectively [33]. Another small Korean study tested the combination of 5-FU, doxorubicin, and mitomycin-C (FAM) in a mixed population of patients with gemcitabine-refractory pancreatic and biliary tumours [34]. Fifteen of the 31 enrolled patients had pancreatic cancer. The results were reported for all patients combined and the median TTP and OS were 2.3 and 6.7 months, respectively. In another study, Blaya *et al*. [35] combined capecitabine (800 mg/m^2 *po bid* days 1-14) with docetaxel (30 mg/m^2 days 1 and 8). There were 3 (12.5%) responses among 24 treated patients and 11 patients showed a decrease in CA 19-9 levels; further results are awaited.

The cyclo-oxygenase 2 (COX-2) pathway is frequently upregulated in pancreatic cancer and treatment with COX-2 inhibitors has shown promising activity in preclinical studies [36]. Two studies have tested the combination of a fluoropyrimidine with the COX-2 inhibitor celecoxib in gemcitabine pretreated patients. In the first study, Milella *et al*. [37] administered 5-FU (200 mg/m^2/day) and celecoxib (400 mg *bid*) continuously until progression. Two of the 17 enrolled patients showed a patient response and the median TTP was 8 weeks. Median survival in this study was 17 weeks and the regimen was well tolerated although 4 patients discontinued celecoxib due to upper gastrointestinal tract toxicity. Pino *et al*. administered capecitabine (1,000 mg/m^2 *po bid* for 2 weeks every 3 weeks) with celecoxib (200 mg *bid* continuously) to 35 patients with gemcitabine-resistant pancreatic or biliary tract cancer [38]. The primary endpoint of the trial was 3-month PFS. This was achieved by 60% of the patients and the median survival was 19 weeks.

Saif *et al*. presented preliminary results of a study of PHY906, a Chinese herbal medicine, in combination with capecitabine at the 2009 ASCO Annual Meeting [39]. Capecitabine was administered at a dose of 1,500 mg *po bid* on days 1-7 and PHY906 at 800 mg *po bid* on days 1-4 on a 14-day cycle. Of the first 25 patients enrolled, 1 (4%) showed a partial response and 4 have survived for more than 6 months. Of note, 7 patients died within a month of enrolment (6 from progressive disease) and one was withdrawn because of severe palmar-plantar erythema. More mature outcome data are awaited.

Camptothecins

Irinotecan is the most commonly used camptothecin analogue in advanced pancreatic cancer (Table 1). Two studies incorporating irinotecan in the IROX [24] and G-FLIP [32] regimens have already been mentioned. The efficacy of irinotecan (150 mg/m^2 every 2 weeks) as a single agent was reported by Yi *et al*. [40]. Thirty three gemcitabine-resistant patients were treated and 3 (9%) partial responses were seen. Median PFS and OS were 2 and 6.6 months and toxicity was acceptable.

A pilot study combining irinotecan (160 mg/m^2) and docetaxel (65 mg/m^2) in a three-weekly schedule had to be abandoned after only 14 patients were enrolled due to excess toxicity, mainly neutropenia, diarrhoea, nausea and vomiting [41]. No responses were seen and the median time to treatment failure was a disappointing 36 days (5.1 weeks). Similarly disappointing results were reported from a dose escalation study of mitomycin-C, docetaxel and irinotecan [42]. No responses were seen among 15 patients treated at the maximum tolerated dose and median PFS and OS were 1.7 and 6 months, respectively. Therefore, despite encouraging preclinical evidence, the combination of irinotecan and docetaxel appears inactive in gemcitabine-resistant pancreatic cancer.

The addition of irinotecan to raltitrexed, was tested in a randomised phase II study by Ulrich-Pur *et al*. [43]. Thirty eight patients were randomised to receive raltitrexed (3 mg/m^2) with or without irinotecan (200 mg/m^2) every 3 weeks. The combination arm was clinically superior with median PFS and OS being 4 and 6.5 months, respectively, compared to 2.5 and 4.3 months in the raltitrexed arm (Table 2). No tests of statistical significance were reported, although the small number of patients enrolled would probably preclude any valid inferences. Toxicity was increased with combination treatment, but grade 3 toxicity was uncommon in this small study and the regimen was well tolerated.

Rubitecan, an orally bioavailable camptothecin derivative, was the subject of the largest study conducted in gemcitabine-resistant pancreatic cancer. Burris *et al*. [44] reported the results of an initial single arm study in which 58 heavily pretreated patients were enrolled. Rubitecan (1.5 mg/m^2 *po* 5 days per week) was reasonably well tolerated, although 34% of the patients required a dose reduction due to toxicity. Median TTP and OS were a modest 1.9 and 3 months, respectively. Subsequently, a large phase III study was launched (Table 2), the results of which have only been reported in abstract form [45]. Four-hundred and nine patients were randomised to treatment with rubitecan or physician's best choice (chemotherapy 89%, supportive care only 11%). There were more responses in the rubitecan arm (11% *vs*. 1%) and the difference in median PFS, although clinically modest, reached statistical significance (1.9 *vs*. 1.6 months). There was no significant difference however, in OS which was 3.5 months in the rubitecan arm compared to 3.1 months in the control arm. The drug manufacturer, SuperGen (Dublin, CA, USA), withdrew an FDA new drug application for rubitecan in 2005 and has since halted clinical development of the agent.

Taxanes

The lack of clinical activity of the docetaxel-irinotecan combination has already been mentioned [41, 42]. These results were echoed in a small study of single agent weekly docetaxel (30 mg/m^2) that enrolled 10 patients and reported no objective responses [46]. Median PFS and OS were 2.5 and 4 months respectively. Similarly, a study of weekly docetaxel (35 mg/m^2) and flavopiridol (80 mg/m^2) was closed early due to excess toxicity and lack of any objective responses in gemcitabine-resistant patients [47].

Paclitaxel has shown some activity in combination with 5-FU (see "Other fluoropyrimidine-based combinations"). A study of weekly paclitaxel (90 mg/m^2) as a single agent in 18 gemcitabine-resistant patients showed good tolerability. One (6%) response was seen and median survival was 17.5 weeks [48]. In summary, the activity of taxanes in this setting appears to be negligible and docetaxel-based regimens, in particular, have been associated with unacceptable levels of toxicity.

Other Chemotherapeutic Combinations

Pemetrexed, lipoplatin, eribulin and regional hyperthermia modulation of cisplatin have all been investigated in gemcitabine-resistant pancreatic cancer (Table 1). Pemetrexed has shown promising activity in combination with oxaliplatin [25] and has also been tested as a single agent. In a study by Boeck *et al*. [49], 52 patients received pemetrexed (500 mg/m^2) every 3 weeks. Two (4%) of patients had a partial response to treatment and toxicity was manageable with a quarter of the patients experiencing grade 3-4 gastrointestinal toxicity. Median PFS and OS were however only 7 and 20 weeks, respectively.

Eribulin is a microtubule-stabilising halichondrin B analogue. Moore *et al*. [50] conducted a small phase II study of eribulin (1.4 mg/m^2 days 1 and 8 every 3 weeks) in gemcitabine-resistant advanced pancreatic cancer. Three (20%) patients showed prolonged stable disease, lasting in excess of 9 months. However, there were no responses among 15 enrolled patients and the study was therefore terminated.

A liposomal formulation of cisplatin, lipoplatin, was originally developed to improve the toxicity profile of cisplatin. Stathopoulos *et al*. [51] performed a dose escalation study of biweekly lipoplatin (25-125 mg/m^2) in combination with gemcitabine (1,000 mg/m^2) in patients whose disease had progressed on previous gemcitabine-based chemotherapy. Two (8%) of the 24 patients showed a partial response and a further 14 (58%) had stable disease for a median duration of 3 months. Non-haematological toxicity was minimal and further evaluation of the combination is planned.

Tschoep *et al*. [52] presented the results of a study of regional hyperthermia combined with biweekly cisplatin (25 mg/m^2 days 1 and 2) and gemcitabine (1,000 mg/m^2) in 22 gemcitabine-refractory patients. Toxicity was minimal with only 3 cases of grade 3 anaemia and no non-haematological toxicity greater than grade 2. The study reached its primary endpoint with a median TTP of 4.2 months and a phase III study of regional hyperthermia-modulated cisplatin-gemcitabine is planned.

Biological Agents

Multiple growth pathways are activated in pancreatic adenocarcinomas. These include the EGFR-RAS-MEK-ERK, the PI3K-AKT-mTOR and the VEGF-VEGFR pathways [53]. Since around 80% of pancreatic adenocarcinomas possess mutations in v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) [54], molecular targeted therapy has always been considered to hold potential for this highly chemoresistant form of cancer. Even so, studies conducted with tipifarnib, a farnesyltransferase inhibitor designed to inhibit KRAS, proved remarkably disappointing [55]. Subsequently, at least in first line therapy, the addition of erlotinib and bevacizumab to standard gemcitabine-based chemotherapy has resulted in only very modestly improved outcomes [4, 7]. Still, it is hoped that, as other key pathways governing the malignant process are identified, new biological agents, such as inhibitors of the Hedgehog [56] and Notch [57] pathways, will be developed which might achieve greater clinical improvements, both in the first and second line setting. Table 3 summarises the available data regarding the use of targeted agents in patients with gemcitabine-refractory metastatic disease.

Table 3. Prospective single arm phase II biological agent trials in gemcitabine-resistant metastatic pancreatic cancer.

Study	Regimen	No. of patients	Partial response + complete response (PR+CR: %)	Median progression-free survival (PFS: months)	Median overall survival (OS: months)
Ignatiadis *et al*. [62]	Gefitinib, docetaxel	26	0	2.1	2.9
Brell *et al*. [63]	Gefitinib, docetaxel	41	2	1.8	4.5
Kulke *et al*. [58]	Erlotinib, capecitabine	30	10	3.4	6.5
Javle *et al*. [59]	Erlotinib, everolimus	16	0	n/a	n/a
Ko *et al*. [60]	Erlotinib, bevacizumab	26	4	1.3	3.4
Dragovich *et al*. [65]	Vatalinib	65	n/a	6-month PFS: 14%	6-month OS: 31%
O'Reilly *et al*. [66]	Sunitinib	77	0	1.3	3.2
Javle *et al*. [59]	Temsirolimus	5	0	n/a	n/a
Garrido-Laguna *et al*. [67]	Sirolimus	n/a	n/a	1.5	n/a
Wolpin *et al*. [68]	Everolimus	33	0	1.8	4.5

n/a: not available

The evidence that erlotinib, an oral tyrosine kinase inhibitor (TKI) inhibiting the epidermal growth factor receptor (EGFR) is effective against pancreatic cancer is far from convincing. In the phase III PA.3 trial conducted in previously untreated metastatic pancreatic cancer, the addition of erlotinib to gemcitabine generated a statistically significant improvement in median survival, although the actual gain was under 2 weeks (6.24 *vs.* 5.91 months, P=0.038) [4]. In gemcitabine-pretreated patients, Kulke *et al*. [58] tested the combination of capecitabine (1,000 mg/m^2 *po bid* days 1-14 every 3 weeks) and erlotinib (150 mg *po od* continuously). Toxicity was significant with mostly grade 3 diarrhoea and skin toxicity leading to dose modifications and delays in two thirds of the 30 enrolled patients. However, 3 partial responses were observed and the median PFS and OS were an encouraging: 3.4 and 6.5 months, respectively.

Erlotinib has also been tested in combination with other biological agents, in the absence of chemotherapy. In a study of erlotinib and everolimus, an oral mammalian target of rapamycin (mTOR) inhibitor, no evidence of efficacy was seen [59]. Out of 16 patients, 7 experienced grade 3 or worse toxicity and progressive disease was noted at the first evaluation point in 15. Similarly, a combination of erlotinib (150 mg *po* daily) and the anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab (15 mg/kg i.v. every 3 weeks) only showed modest activity. One (4%) of 26 patients showed a partial response in a small phase II study with a further 7 (27%) having stable disease for at least 6 weeks [60]. Median TTP and OS were only 1.3 and 3.4 months, respectively.

Gefitinib is another TKI targeting the EGFR. In preclinical studies it showed evidence of activity, inhibiting pancreatic cell growth, invasion and colony formation [61]. However, two phase II studies of gefitinib combined with docetaxel in gemcitabine-refractory patients showed limited efficacy. Ignatiadis *et al*. [62] administered docetaxel (75 mg/m^2 every 3 weeks) and gefitinib (250 mg *po od* continuously) to 26 patients. No responses were seen, the median TTP was 2.1 months and the median survival a disappointing 2.9 months. Brell *et al*. evaluated the same regimen in 41 patients [63]. They reported unacceptably high levels of febrile neutropenia and disappointing efficacy with median TTP and OS of 1.8 and 4.5 months respectively. These studies reflect the poor results seen in other taxane-based regimens tested in gemcitabine-refractory pancreatic cancer; whether combining gefitinib with a more active agent will improve outcomes is currently unknown.

Bevacizumab has also been evaluated in a small randomised study with docetaxel in gemcitabine-resistant disease [64]. Thirty patients were randomised to bevacizumab (10 mg/kg every 2 weeks) with or without weekly docetaxel (35 mg/m^2). Five patients experienced serious adverse events (3 thromboembolic episodes and 2 bowel perforations). Efficacy was minimal with only one response seen in the combination arm. Median PFS was 1.4 and 1.5 months for bevacizumab and bevacizumab-docetaxel respectively. The corresponding median OS was 5.9 and 4 months (P=0.8). Recruitment was halted after the first stage as the target median PFS of 4 months in either arm was not reached.

Similar modest efficacy has been noted with other VEGF targeting agents. Vatalinib, an oral VEGF receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR) TKI, was evaluated in a single arm phase II study. Sixty-five patients received vatalinib in doses up to 750 mg *po bid* with good tolerability. The 6-month PFS and OS rates were 14% and 31%, respectively, which met the study's primary endpoint and was considered promising [65]. Sunitinib is a multi-targeted TKI that primarily inhibits VEGFR and PDGFR. In a phase II study in patients that had previously received gemcitabine, either in the adjuvant or metastatic setting, and had relapsed or progressive disease, sunitinib (50 mg *po od* 4weeks on/2 weeks off schedule) was administered to 77 patients [66]. The majority (86%) of patients received only a single 6-week cycle of treatment, mainly due to rapid disease progression. Median PFS and OS were disappointing at 1.3 and 3.2 months, respectively.

mTOR inhibitors, when used as single agents appear to be inactive in gemcitabine-resistant pancreatic cancer. A trial of temsirolimus (25 mg i.v. weekly) was halted after only 5 patients were enrolled. No responses were seen and 2 patients died within a month of enrolment, one from a haemorrhagic stroke that could be related to the study medication [59]. Sirolimus was associated with a median PFS of 1.5 months and a 6-month survival rate of 20% in a study by Garrido-Laguna *et al*. [67]. Finally, everolimus (10 mg *po od*) also exhibited minimal activity a 33-patient phase II study with median PFS and OS of 1.8 and 4.5 months. respectively [68].

In summary, although limited by small patient numbers, enrolment of heavily pretreated patients and use of combinations with inactive agents such as docetaxel, the available evidence regarding biological agents tested to date in gemcitabine-resistant pancreatic cancer is mostly disappointing.

Performance Status and Toxicity Considerations

It should be kept in mind that almost all the studies summarised in this review restricted eligibility to patients with good performance status (PS). The majority of enrolled patients had a WHO PS of 0 or 1, with a minority having a PS of 2. Unfortunately, the small number of patients in each study precludes any analysis of differential efficacy or toxicity in patients with a PS of 2 compared to patients with better PS and such data have not been reported. It should be noted however, that poor PS is an established adverse prognostic factor in gemcitabine-refractory pancreatic cancer [69]. At present, best supportive care should be

the preferred option in such patients, a position endorsed by professional guidelines [8].

Conclusions and Future Directions

Pancreatic cancer remains a highly chemoresistant malignancy carrying an extremely poor prognosis. For the past decade gemcitabine has been the standard of care for first line treatment of metastatic disease, offering a modest prolongation in survival. However, improvements in diagnosis and earlier intervention with chemotherapy, alongside better supportive care measures over the same time period, have resulted in increasing numbers of patients that remain fit and request second-line treatment following progression on gemcitabine. The needs of these patients remain essentially unmet. Dozens of small studies have shown some hints of activity, with oxaliplatin-fluoropyrimidine combinations appearing the most promising. Second line trials conducted to date are fraught with problems of small patient numbers, while comparisons between trials are made impossible by incomplete information regarding performance status and disease stage, factors that are well known to impact on survival irrespective of treatment. Further randomised trials are much needed. In considering the design of such trials, experience in testing the OFF regimen demonstrated well the difficulties of randomisation where the standard arm is best supportive care.

As the molecular pathways governing pancreatic cancer are unravelled, novel targeted therapies may offer the greatest promise for this disease either given alone, combined with one another, or with cytotoxic agents. Of all human cancers, pancreatic adenocarcinoma has the highest incidence of KRAS mutation (more than 80%) and there is evidence to suggest that signalling through KRAS dominates tumourigenesis. The two key signalling pathways downstream of KRAS are Raf/MEK/ERK and PI3K/AKT/mTOR. Dual blockade of these pathways is now possible with new small molecule inhibitors available, by combining for example a MEK1/2 inhibitor and an mTOR kinase inhibitor. In addition, other pathways such as those involved in notch and hedgehog signalling are implicated in pancreatic carcinogenesis and are the focus of novel drug discovery programmes. The first studies testing some of these targeted agents either alone or in combination are now underway and their results eagerly awaited to determine whether mechanism-driven treatment will offer much needed improved outcomes for this chemoresistant cancer.

Conflict of interest The authors have no potential conflicts of interest

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