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TOPIC HIGHLIGHT

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Recent developments in palliative chemotherapy for locally advanced and metastatic pancreas cancer

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Abstract

In spite of advances made in the management of the other more common cancers of the gastrointestinal tract, significant progress in the treatment of pancreatic cancer remains elusive. Nearly as many deaths occur from pancreatic cancer as are diagnosed each year reflecting the poor prognosis typically associated with this disease. Until recently, the only treatment with an impact on survival was surgery. In the palliative setting, gemcitabine (Gem) has been a standard treatment for advanced pancreatic cancer since it was shown a decade ago to result in a superior clinical benefit response and survival compared with bolus 5-fluorouracil. Since then, clinical trials have explored the pharmacokinetic modulation of Gem by fixed dose administration and the combination of Gem with other cytotoxic or the biologically "targeted" agents. However, promising trial results in small phase Ⅱ trials have not translated into survival improvements in larger phase Ⅲ randomized trials in the advanced disease setting. Two trials have recently reported modest survival improvements with the use of combination treatment with Gem and capecitabine (United Kingdom National Cancer Research GEMCAP trial) or erlotinib (National Cancer Institute of Canada Clinical Trials Group PA.3 trial). This review will focus on the use of systemic therapy for advanced and metastatic pancreatic cancer, summarizing the results of several recent clinical trials and discuss their implications for clinical practice. We will also discuss briefly the second-line chemotherapy options for advanced pancreatic cancer.

Key words: Adjuvant therapy; Chemotherapy; Palliative therapy; Pancreas cancer; Radiotherapy

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INTRODUCTION

Pancreatic cancer is responsible for approximately 5% of cancer-related deaths and is the eighth most common cause of cancer-related death for both genders combined worldwide[1]. Recent estimates indicate that approximately 42 000 new cases and deaths are expected to occur in the United States during 2009. For all the stages combined, the 1- and 5-year survival rates are only 23% and 5%, respectively[2].

The prognosis is even poorer for patients with advanced pancreatic cancer. At the time of diagnosis, approximately half of the patients have metastases, and their median overall survival (OS) with treatment is around 6 mo; whe-

reas approximately one third of patients diagnosed with locally advanced disease have an OS ranging between 6 and 9 mo[3]. Only 15%-20% of patients are eligible for surgery at diagnosis[3]. Only about 20% of surgically resected patients with localized disease will survive 5 years. There is a clear need for better systemic treatments.

This review will summarize and discuss the various clinical trials of chemotherapy for locally advanced and metastatic pancreatic cancer, including the more recent trials, which have investigated the novel targeted agents.

PALLIATIVE CHEMOTHERAPY FOR ADVANCED PANCREATIC CANCER

Patients with metastatic or locally advanced inoperable pancreatic cancer are enrolled in clinical trials as a group, although these patients have different prognoses. The role of radiation therapy for patients with locally advanced disease remains controversial. In addition to a survival benefit, the palliative role of chemotherapy in addition to best supportive care compared to supportive care alone has been demonstrated in advanced pancreatic cancer[4-6]. Patients treated with 5-fluorouracil (5-FU) based chemotherapy had an OS of 6-10 mo compared with 2-3.5 mo in patients who did not receive chemotherapy. Glimelius *et al*[4] also reported that quality of life (QOL) was better, and quality-adjusted survival time was longer, for patients who were randomized to chemotherapy (median of 4 mo *vs* 1 mo, $P = 0.01$) since gemcitabine (Gem) was established as a standard therapeutic agent.

Single agent Gem

The improvement in survival with 5-FU-based chemotherapy compared to best supportive care, and of Gem compared to bolus 5-FU has established Gem as the standard treatment in advanced or metastatic pancreatic cancer[7]. In phase Ⅱ studies, single-agent Gem has shown modest response rates (RR) of 6%-11% with disease stabilization occurring in a further 19%-32%[8]. The toxicities observed with Gem include bone marrow suppression, lethargy, a flu-like syndrome, nausea and vomiting, and peripheral edema. Several trials have attempted to improve upon the efficacy of Gem.

Fixed dose Gem: The administration of Gem usually involves a fixed dose rate (FDR) of 10 mg/m^2 per min. Gem is a pro-drug that is converted to its active tri-phosphate form intracellularly. FDR infusion maximizes the intracellular concentrations of the phosphorylated forms of Gem[9].

In a randomized phase Ⅱ trial[10], Gem at FDR infusion led to a higher RR and better survival, although the primary end point of time to treatment failure (TTF) was similar for both arms. (2.1 mo for FDR Gem *vs* 1.8 mo, $P = 0.09$). The median survivals were 8.0 and 5.0 mo, and the 1-year survivals were 28.8 and 9%, for both arms, respectively. The incidence of hematological toxicity, particularly grade 3-4 neutropenia, was higher in the FDR Gem arm (48.8% *vs* 26.5%).

However in a phase Ⅲ trial by the Eastern Cooperative Oncology Group (ECOG)[11], the FDR of Gem or GemOx [Gem and oxaliplatin (Ox)] did not meet the survival superiority endpoint of the trial compared to standard infusion Gem. Table 1 shows the efficacy results from this trial.

Table 1 Progression-free and overall survival analyses from the ECOG 6201 trial[11]

Parameter	PFS		OS	
	Median (mo)	Log-rank *P*	Median (mo)	Log-rank *P*
All eligible patients ($n = 824$)	2.9		5.6	
Gem ($n = 275$)	2.6		4.9	
FDR Gem ($n = 277$)	3.5	0.09	6.2	0.15
GemOx ($n = 272$)	2.7		5.7	

PFS: Progression-free survival; OS: Overall survival; ECOG: Eastern Cooperative Oncology Group; Gem: Gemcitabine; GemOx: Gem and oxaliplatin.

Gem-based combination chemotherapy

Despite promising phase Ⅱ trials, the combination of Gem with other cytotoxic drugs has not been proved to be superior to Gem alone in survival (Table 2).

Gem and FU: Phase Ⅲ trials of Gem plus FU compared with single-agent Gem in patients with advanced disease have not shown any benefit in terms of survival[12,13]. In a phase Ⅲ ECOG trial, 322 patients with advanced pancreatic cancer were randomized to Gem alone *vs* Gem combined with FU. OS was 5.4 mo for Gem alone and 6.7 mo for Gem plus FU ($P = 0.09$). Progression-free survival (PFS) for Gem alone was 2.2 mo, compared with 3.4 mo for Gem plus FU ($P = 0.022$).

Gem and capecitabine: The combination of capecitabine and Gem (GemCap) has shown promising clinical activity in phase I and Ⅱ clinical studies in advanced pancreatic cancer patients[14,15]. A phase Ⅲ trial conducted by Herrmann *et al*[16] also showed positive results for good performance status (PS) patients. Of 319 patients in the study, median OS, the primary end point, was 8.4 and 7.2 mo in the combination and Gem alone arms, respectively ($P = 0.234$). In addition, there was no statistically significant difference in PFS between the arms (4.8 mo *vs* 4.0 mo, $P = 0.0207$). Only the subgroup analysis of patients with good performance status [Karnofsky performance status (KPS) score of 90-100] have shown significant prolongation of median OS in the GemCap group compared with the control group (10.1 mo *vs* 7.4 mo, respectively, $P = 0.014$)[16].

In the more recently reported United Kingdom Phase Ⅲ trial[17] (UK NCRI study), a higher dose intensity of Gem and capecitabine was used than in the previous trial. Capecitabine dose was approximately 44% higher, and the Gem dose in the combined arm was approximately 12% higher. The dose of Gem in the control arm was identical in the two trials. Median OS was shown to be significantly superior in the GemCap group compared with the Gem group (7.4 mo *vs* 6 mo, respectively, $P = 0.014$), as were the ORR (14% *vs* 7%, respectively, $P = 0.001$) and

Table 2 Phase Ⅲ trials of gemcitabine doublets

Phase Ⅲ trial	Combination	OS (mo)	*P*	PFS (mo)	*P*
Berlin *et al*[12] (*n* = 322)	Gem + FU	6.7	0.09	3.4	0.022
	Gem	5.4		2.2	
Herrmann *et al*[16] (*n* = 319)	Gem + Cap	8.4	0.234	4.8	0.0207
	Gem	7.2		4.0	
Heinemann *et al*[19] (*n* = 219)	Gem + Cisplatin	7.6	0.12	5.3	0.053
	Gem	6.0		3.1	
Colucci *et al*[20] (*n* = 107)	Gem + Cisplatin	6.9	0.48	5	0.048
	Gem	4.6		2	
Louvet *et al*[23] (*n* = 326)	GemOx	9.0	0.13	5.8	0.04
	Gem	7.1		3.7	
Poplin *et al*[11] (*n* = 824)	GemOx	5.7	0.09	2.7	0.15
	Gem	4.9		2.6	
	Gem FDR	6.2		3.5	
Rocha Lima *et al*[27] (*n* = 342)	IRINOGEM	6.3	0.789	3.5	0.352
	Gem	6.6		3.0	
O'Reilly *et al*[29] (*n* = 339)	Gem + Exatecan	6.7	0.52	3.9	0.22
	Gem	6.2		4.0	

FU: Fluorouracil.

the 1-year survival rates (26% and 19%, respectively). Although, higher doses of chemotherapy were used in this study, there was no significant difference in the frequency of grade 3 or 4 adverse events between the two trials. These data were presented in 2005. However, the final results of this trial have not been reported and a full manuscript has not been produced.

Additionally, Bernhard *et al*[18] assessed the clinical benefit response (CBR) and QOL in patients treated with GemCap or Gem alone. CBR was defined as improvement from baseline for 4 consecutive weeks in pain (pain intensity or analgesic consumption) and KPS, stability in one but improvement in the other, or stability in pain and performance status but improvement in weight. Of 319 patients, 19% of patients treated with the combination regimen and 20% of patients treated with Gem alone experienced a CBR, with a median duration of 9.5 and 6.5 wk, respectively ($P = 0.02$). There was no treatment difference in QOL ($n = 311$) between the two treatment arms. Regardless of their initial condition, some patients experienced an improvement in QOL on chemotherapy by symptom control; however, this was followed by a worsening 1-2 mo before treatment failure (all $P < 0.05$)[18].

Gem and platinums: A recent randomized phase Ⅲ trial evaluating Gem with or without cisplatin in patients with advanced pancreatic cancer demonstrated a trend toward increased OS (7.6 mo *vs* 6.0 mo, $P = 0.12$) and PFS in the combination arm relative to the control arm but these differences were not statistically significant[19]. Also, there was no significant difference in QOL between the arms and only nausea and vomiting were significantly increased in the combination arm (22.2% *vs* 5.8%, $P = 0.002$). Similarly, another randomized study did not show a benefit in survival for combination treatment (6.9 mo *vs* 4.6 mo, $P = 0.48$) despite a marked improvement in response rate (26.4% *vs* 9.2%, $P = 0.02$)[20].

On the basis of published preclinical *in vitro* synergy data between Gem and Ox[21], the French Multidisciplinary Clinical Research Group in Oncology (GERCOR) has conducted a phase Ⅱ study in 64 patients with advanced or metastatic pancreatic cancer[22]. The encouraging results observed with GemOx in this phase Ⅱ study has prompted the initiation of a phase Ⅲ trial, conducted by both GERCOR and the Italian Group for the Study of Gastrointestinal Tract Cancer (GISCAD). In this phase Ⅲ study, GemOx was superior in terms of PFS (5.8 mo *vs* 3.7 mo, $P = 0.04$), RR (26.8% *vs* 17.3%, $P = 0.04$) and clinical benefit (38.2% *vs* 26.9%, $P = 0.03$)[23] in both the metastatic and locally advanced population. The 1-year survivals observed in both arms of the study were impressive (34.7% and 27.8%, respectively, $P = 0.22$). However, median OS did not significantly improve (9.0 mo *vs* 7.1 mo, $P = 0.13$). For patients with locally advanced disease, median OS was identical in both arms (10.3 mo), whereas in patients with metastatic disease, median OS was 8.5 and 6.7 mo for GemOx and Gem alone, respectively ($P = 0.17$)[23]. The identical OS in patients with locally advanced disease and failure of this study to demonstrate the statistical significance of its primary end point has been attributed to the assignment of some patients to chemoradiotherapy after 3 mo of chemotherapy. Thirty percent and 32% of patients in the Gem and GemOx arms, respectively, presented with locally advanced disease. Chemoradiotherapy was recommended after 3 mo of chemotherapy in the case of stable disease or response, at the discretion of each investigator. Sixteen out of 40 (40%) and 11 out of 33 (33.3%) patients in the GemOx and Gem arms, respectively, received chemoradiotherapy. The incidence of grade 3-4 thrombocytopenia, vomiting and peripheral sensory neuropathy was increased in the combination arm[23]. An ECOG study[11] was designed to compare the survival impact of single-agent Gem *vs* Gem FDR or GemOx in metastatic or locally advanced pancreatic cancer, and performance status 0 to 2. Of 824 patients enrolled, there was no significant difference in median survival and PFS among the 3 treatment arms (Table 1). A meta-analysis of 5 randomized trials (two oxaliplatin-based and three

cisplatin-based Gem combinations) by Heinemann *et al*[24] demonstrated a significant improvement in ORR and PFS in 2 trials, while the level of significance was not reached in the other 3 trials. The platinum-based combination regimens consistently prolonged OS. However, none of the individual trials showed a statistically significant superiority compared to Gem alone. A significant improvement in OS was detected only when a combined analysis of the five trials was performed (HR = 0.85, $P = 0.010$).

Gem and topoisomerase inhibitors: Irinotecan alone has a response rate of 9% in advanced pancreatic cancer[25]. In a phase Ⅱ, multicenter, single-arm study with irinotecan and Gem (IRINOGEM), 11/45 patients (24%) had 50% or greater reductions in tumor area with a RR of 20% (95% CI, 8%-32%). CA 19-9 was found to decrease during therapy in 50% of patients and was reduced by ≥ 50% in 30% of patients[26]. There were significant ($P < 0.001$) correlations between proportional changes in CA 19-9 and radiographic changes in the tumor area. Median TTP, median survival and 1-year survival rate were modest at 2.8 mo, 5.7 mo and 27%, respectively. Severe toxicities were uncommon and primarily limited to grade 4 neutropenia (2%), grade 4 vomiting (2%), and grade 3 diarrhea (7%)[26]. This phase Ⅱ data was followed by a phase Ⅲ randomized study conducted by Rocha Lima *et al*[27] to compare the OS of 180 patients randomly assigned to IRINOGEM ($n = 173$) *vs* Gem ($n = 169$). Unfortunately, the combination was not found to improve OS (6.3 mo *vs* 6.6 mo, $P = 0.789$), although the combination had a significantly better tumor RR (16.1% *vs* 4.4%, $P < 0.001$)[27]. Median TTP was 3.5 mo for the IRINOGEM group *vs* 3.0 mo for the Gem group ($P = 0.352$). However, subset analyses in patients with locally advanced disease suggested a TTP advantage with IRINOGEM *vs* Gem (7.7 mo *vs* 3.9 mo). CA 19-9 progression was positively correlated with tumor progression as shown in the previous phase Ⅱ trial conducted by the same author. The incidence of grade 3 diarrhea was higher in the IRINOGEM group but grade 3 to 4 hematologic toxicities and QOL measures were similar[27].

Another topoisomerase inhibitor exatecan (DX-8951f) was studied in a randomized phase Ⅲ trial and was shown to be inferior to Gem in RR and improvement in QOL[28]. Furthermore, the combination of exatecan and Gem failed to show any significant survival benefit over Gem alone in a phase Ⅲ study (6.7 mo *vs* 6.2 mo, $P = 0.52$)[29]. Patients in the combination treatment arm experienced significantly more grade 3-4 toxicity, in particular neutropenia (30% *vs* 15%, $P = 0.001$), thrombocytopenia (17% *vs* 5%, $P = 0.004$) and vomiting (11% *vs* 5%, $P = 0.04$)[29].

The oral topoisomerase I inhibitor rubitecan (9NC) has also been tested in pancreatic cancer in phase Ⅰ/Ⅱ trials[30,31]. In the phase Ⅱ trial of 19 enrolled patients, an objective response was documented in 4 of the 14 evaluable patients (28.6%). Overall median survival was 21 wk and the 1-year survival was 16.7%. Toxicity leading to temporary discontinuation of 9NC was encountered in seven patients (36.8%), all related to a prior dose increase, while milder toxicity was observed in eight patients (42.1%)[31].

Gem and taxanes: Although the taxanes (docetaxel and paclitaxel) have both single-agent activity and activity in combination chemotherapy in advanced pancreatic cancer, they are associated with significant toxicity, particularly myelosuppression. In a phase Ⅰ/Ⅱ study of Gem with docetaxel, the dose-limiting toxicity was grade 3-4 neutropenia[32]. Subsequent phase Ⅱ combination studies have reported RR of 12%-18% and median survivals of 4.7-8.9 mo[33-35]. The incidence of grade 3-4 neutropenia was improved by the addition of prophylactic GCSF (31%) or ciprofloxacin (48%), although these studies still reported an incidence of febrile neutropenia in 12% of patients[33,34].

Gem with other agents: Gem has also been investigated in a multidrug combination chemotherapy regimen. A very small randomized study comparing the combination of cisplatin, epirubicin, FU and Gem (PEFG regimen, $n = 51$) to Gem alone ($n = 46$) showed better 4-mo PFS (primary end point) (60% *vs* 28%) and RR (38.5% *vs* 8.5%, $P = 0.008$)[36] in the PEFG group than in the control group. Both the 1-year OS (38.5% *vs* 21.3%, $P = 0.119$) and the median OS (5.4 mo *vs* 3.3 mo, $P = 0.0033$) were impressive in the PEFG group. There was no significant difference in QOL between the treatment arms, although there was a higher CBR in the PEFG arm (65% *vs* 25%, $P = 0.0139$). However, grade 3-4 neutropenia (43% *vs* 14%, $P = 0.0001$) and thrombocytopenia (30% *vs* 1%, $P = 0.0001$) occurred more frequently in the PEFG arm. Subsequently, this regimen was modified by increasing the dose intensity of cisplatin and epirubicin (both at 30 mg/m^2 every 14 d) and of Gem (at 800 mg/m^2 every 14 d) in an attempt to further improve activity and efficacy, to reduce toxicity and to yield a schedule more suitable to the patient[37]. When compared with 84 patients treated with classical PEFG at the same institution, dose-intense PEFG was not inferior in terms of PFS at 6 mo (63% *vs* 57%), 1-year OS (48% *vs* 42%) and RR (49% *vs* 49%); it allowed an increase in dose intensity for Gem of 32%, for cisplatin and epirubicin of 36% (FU reduced by 3%) which significantly reduced grade 3-4 hematological toxicity (neutropenia: 26% *vs* 86%, $P < 0.00001$; thrombocytopenia: 4% *vs* 58%, $P < 0.00001$) and reduced the number of outpatient accesses by one-third[37].

Emerging role of the novel targeted agents in pancreatic cancer

A better understanding of the biology of cancer has led to the development of novel agents targeting pathways of cancer cell survival. Since Gem has been considered a standard treatment for advanced pancreatic cancer for the past decade, clinical trials have explored the combination of Gem and biological "targeted" agents. However, despite their promise in preclinical studies, most of the clinical trials with the newer agents have not shown survival advantage when compared with standard Gem. A questionable exception is the combination of Gem and erlotinib which showed superiority in median survival compared to Gem alone, but only a net gain of two weeks

Table 3 Phase Ⅰ/Ⅲ trials of gemcitabine in combination with novel targeted therapies

	Combination	OS (mo)	*P*	PFS (mo)	*P*	ORR (%)	SD (%)
Phase Ⅱ trial							
Xiong *et al*[41] (*n* = 61)	Gem + Cetuximab	7.1		3.8		12.2	63.4
Fogelman *et al*[47] (*n* = 50)	GemOx + BEV	12.1		NR		NR	39
Kim *et al*[48] (*n* = 82)	GemOx + BEV	8.1		5.7		11.3	NR
Ko *et al*[49] (*n* = 57)	Gem + Cetuximab + BEV	NR		3.5		10.7	29
	Cetuximab + BEV			1.8		0	24
Kindler *et al*[50] (*n* = 139)	Gem + BEV + Erlotinib	7.8		5.0		23	49
	Gem + BEV + Cetuximab	7.2		5.1		18	45
Phase Ⅲ trial							
Moore *et al*[40] (*n* = 569)	Gem + Erlotinib	6.37	0.038	NR	0.004		
	Gem	5.91					
Philip *et al*[43] (*n* = 735)	Gem + Cetuximab	6.5	0.14	3.5	0.058		
	Gem	6.0		3.0			
Kindler *et al*[45] (*n* = 602)	Gem + BEV	5.7	NS	4.8	NS		
	Gem	6.0		4.3			
Vervenne *et al*[46] (*n* = 607)	Gem + BEV	7.1	NS	4.6	0.0002		
	Gem	6.0		3.6			

ORR: Overall response rate; SD: Stable disease; NR: Not reported; NS: Not significant; BEV: Bevacizumab; Gem: Gemcitabine; Gem FDR: Gemcitabine fixed-dose rate; GemOx: Gemcitabine 1000 mg/m^2 iv over 100 min on day 1 plus oxaliplatin 100 mg/m^2 on day 2 every 14 d.

was observed, questioning the true clinical significance of this superiority[5] (Table 3).

Gem based chemotherapy with novel targeted agents

Gem and erlotinib: Preclinical synergy with Gem and erlotinib in inducing apoptosis in pancreatic xenograft models was demonstrated[38], and a phase I study established the dose of erlotinib for single-agent daily dosing to be 150 mg/d, with which the incidence of severe diarrhea and/or skin rash was unacceptably high[39]. In a phase Ⅲ trial by Moore *et al*[40], 569 patients with locally advanced and metastatic pancreatic cancer were randomly assigned to receive erlotinib plus Gem *vs* Gem alone. The study showed statistically significant improvements in OS (6.37 mo in the erlotinib arm and 5.91 mo in the control arm, $P = 0.038$) and PFS ($P = 0.004$). Median survival in the erlotinib group was 6.24 mo and the 1-year survival rate was 23% compared with 5.91 mo and 17% in the control arm. There was a slight increase in the incidence of grade 3-4 skin rash and diarrhea (6% *vs* 1%) in the group receiving erlotinib, although there was no overall difference in QOL between the arms. As in studies of anti-EGFR agents in colorectal cancer, the presence of rash was associated with a higher likelihood of achieving disease control[40] ($P = 0.05$). This study did not require EGFR positivity to be demonstrated prior to study entry and the overall rate of EGFR expression observed was 57%, which was lower than has been reported in previous studies[41,42]. A subgroup analysis by EGFR status suggested a trend towards benefit from erlotinib regardless of EGFR status, but there was inadequate power to show statistical significance.

Gem and cetuximab: In a phase Ⅱ study[41], 41 patients with EGFR expressing advanced pancreatic cancer were treated with the combination of Gem and cetuximab. A reasonable RR of 12.2% was reported, with a further 63.4% of patients achieving disease stabilization. These results led to a randomized phase Ⅲ trial[43] undertaken by The South Western Oncology Group (SWOG, S0205), the results of which were presented at the 43rd American Society of Clinical Oncology (ASCO) Annual Meeting in 2007 and did not show any survival benefit[43]. Seven hundred and thirty five patients were enrolled between January 2004 and April 2006. The median survival was 6 mo in the Gem arm and 6.5 mo in the Gem plus cetuximab arm for an overall HR of 1.09 (95% CI: 0.93-1.27, $P = 0.14$). The corresponding PFS was 3.0 and 3.5 mo, for the Gem and Gem-cetuximab arms, respectively (HR: 1.13; 95% CI: 0.97-1.30, $P = 0.058$). The unconfirmed responses yielded 14% in the Gem arm and 12% in the Gem-cetuximab arm.

Gem and bevacizumab: Another targeted agent with promising efficacy in pancreatic cancer is bevacizumab which was studied in combination with Gem in a phase Ⅱ trial that resulted in a RR of 19%[44]. However, the results of the US Cancer and Leukemia Group B (CALBG) phase Ⅲ randomized trial of Gem with or without bevacizumab did not reveal any improvement in survival upon addition of bevacizumab[45]. Median OS in the bevacizumab arm *vs* the control arm was 5.7 mo *vs* 6.0 mo (95% CI: 4.9-6.5 mo *vs* 5.0-6.9 mo) and PFS of 4.8 mo *vs* 4.3 mo, respectively (95% CI: 4.3-5.7 mo *vs* 3.8-5.6 mo). This result did not prevent completion of a similar, Roche sponsored trial, AVITA, in which 607 patients with metastatic pancreatic cancer were randomized to Gem and erlotinib with or without bevacizumab[46]. There was no significant prolongation of survival with the addition of bevacizumab, although disease-free survival (DFS) was statistically significantly improved (from 3.6 to 4.6 mo). Bevacizumab was reported to be safe in this combination, despite an increase in the incidence of epistaxis, hypertension and proteinuria. Interestingly, there was no reported increase in thrombotic events with bevacizumab[3]. The AVITA study suggests that antiangiogenic strategies may have merit in the treatment of

advanced pancreatic cancer, although the margin of benefit with bevacizumab is modest.

Two phase Ⅱ trials were presented at the 2009 ASCO Gastrointestinal Cancer Symposium which evaluated the efficacy of Gem in combination with biologic agents. Fogelman *et al*[47] reported the final results of a 3-drug combination consisting of Gem, Ox and bevacizumab in 50 patients with advanced pancreatic cancer. This triple drug combination achieved 1 and 2-year survival rates of 40% and 16%, respectively with a high response rate of 39%[47]. In addition, this regimen demonstrated a higher RR and longer median survival compared to a previously reported Gem and Ox study[23]. Of note, there was a correlation between CA 19-9 levels and median survival. Another phase Ⅱ trial[48] assessing the combination of GemOx plus bevacizumab included 82 patients with advanced pancreatic cancer. This study showed 6-mo survival of 65.0% (95% CI: 53.5%-75.3%), median survival of 8.1 mo (95% CI: 6.5-9.3 mo) and median TTP of 5.7 mo (95% CI: 4.4-6.4 mo).

On the other hand, Gem with a dual monoclonal antibody regimen was disappointing. Ko *et al*[49] designed a phase Ⅱ trial to evaluate the efficacy of dual EGFR/VEGF monoclonal antibodies cetuximab and bevacizumab with or without Gem. Fifty-seven patients received dual antibodies. Overall RR was only 10.7% in the Gem arm and OS data has not been presented yet[49]. The above results were confirmed by another phase Ⅱ trial by Kindler *et al*[50]. One hundred and thirty-nine patients with locally advanced pancreatic cancer received Gem, bevacizumab and erlotinib or Gem, bevacizumab and cetuximab[50]. Interestingly, a correlation between early hypertension and response to treatment was observed. There was no significant difference between the two arms in either OS or PFS. Therefore, cetuximab or bevacizumab is not recommended for the treatment of advanced pancreatic cancer in the current clinical setting outside of an investigational trial.

Other combined regimens

There have been very few attempts to address the role of alternative cytotoxic agents other than Gem in the first-line setting which may represent better platforms for the addition of targeted therapies. One such study conducted by Ducreux *et al*[51] evaluated the efficacy of oxaliplatin alone (OXA), infusional FU alone (FU) and an oxaliplatin/infusional 5-FU combination (OXFU) in the phase Ⅱ setting. 90% of patients had metastatic disease (81% with liver metastases) and 83% of patients had PS 0-1. Median TTP and OS were higher in the combination arm (4.2 and 9.0 mo, respectively) than either of the single-agent arms (OXA, 2.0 and 3.4 mo; FU, 1.5 and 2.4 mo, respectively). Response rate was 10% in the OXFU arm and the safety profile was encouraging[51].

In the FFCD 0301 trial[52], a large phase Ⅲ trial presented in the first-line setting, 202 patients with advanced pancreatic cancer were randomized to either FU and leucovorin plus cisplatin followed by Gem or *vice versa*. Patients received therapy until progression after which they could cross to the opposite arm. After a median follow-up of 44 mo, the majority of patients (n = 192) died. There was no significant difference in survival between the two arms. One-year and two-year survival figures were also identical between the Gem and FU plus cisplatin arms. Although it is unlikely that FU and cisplatin will replace Gem due to toxicity concerns, these data provided the rationale for non-Gem containing regimens in the first-line setting. One may consider a pharmacogenomic profile in the future to select either therapy.

EndoTAG-1 is a novel cationic liposomal formulation of paclitaxel. It increases the microvascular permeability probably due to vascular damage. Manipulation of the blood-tumor barrier with EndoTAG-1 can increase the effectiveness of conventional chemotherapy. The combination of Gem plus liposomal paclitaxel at three different dose levels (11, 22, or 44 mg/m^2) was compared to Gem alone in 200 patients with metastatic pancreatic cancer[53]. Preliminary results were presented at the 2009 ESMO meeting. This regimen achieved a disease control rate of 53%-69% depending on the dosage of paclitaxel. Median PFS was 18, 20, and 19 wk, respectively, in the Gem/EndoTAG-1 low, medium, and high dose groups, compared with 12 wk in the Gem monotherapy group. Median OS was 7.2 mo with Gem alone *vs* 8.4, 8.7, and 9.4 mo with Gem plus low, medium, and high dose EndoTAG-1. Twelve-month survival rates were 17% with Gem alone *vs* 22%, 36% and 33% for Gem plus low, medium and high dose EndoTAG-1.

The results of a randomized phase Ⅱ trial of 3 different regimens in patients with advanced pancreatic cancer suggested that capecitabine plus Ox is comparable to Gem combined with either capecitabine or Ox[54]. A phase Ⅱ trial conducted by Burtness *et al*[55] confirmed the activity of another non-Gem regimen. Ninety-two patients with advanced pancreatic cancer were randomly assigned to receive irinotecan/docetaxel (Arm A) or irinotecan/docetaxel/cetuximab (Arm B). Median OS were reported to be 6.5 (95% CI: 4.8-8.6 mo) and 7.4 mo (95% CI: 4.4-10.7 mo) in Arm A and B, respectively. However, this triple regimen was associated with high rates of grade 3-4 neutropenia and diarrhea[55].

Other agents

Numerous studies employing other novel targeted agents are currently being developed. The CALGB presented the results of a single-arm phase Ⅱ study of sunitinib for patients with advanced pancreatic cancer who had previously been treated with Gem-based therapy. No responses were reported in 77 treated patients, and stable disease in only 7 patients[56]. The California consortium reported similar disappointing results with sorafenib when combined with Gem[57]. In this randomized study, chemo-naive pancreatic cancer patients received sorafenib as a single agent or in combination with Gem. No responses resulted with sorafenib alone and the median survival in the Gem plus sorafenib arm was only 6 mo. Wolpin *et al*[58] treated 31 Gem-refractory pancreatic cancer patients with everolimus, an oral mTOR inhibitor. Although the agent was tolerable, there was no response and disease stability

was uncommon. These targeted agents do not merit further study in pancreatic cancer due to their insufficient anti-tumor activity. Other targeted agents, which have been tested in pancreatic cancer and not found to add any survival benefit, include the farnesyl transferase inhibitor tipifarnib[59,60] and the matrix metalloproteinase inhibitors marimastat[61-63] and BAY 12-9566[64].

Another new agent, AMG 655, is a fully humanized monoclonal antibody that targets human death receptor 5 (DR5), activates caspases, and induces apoptosis in sensitive tumor cells. In pancreatic cancer xenografts, the anti-tumor activity of AMG 655 was enhanced by adding Gem. In a phase I trial[65], patients with metastatic pancreas cancer were enrolled into sequential cohorts of 3- or 10-mg/kg AMG 655 iv on days 1 and 15 plus Gem 1000 mg/m^2 iv on days 1, 8, and 15 every 28 d. Best overall tumor response assessed by RECIST criteria showed that 3 (23%) patients had partial responses, 6 (46%) had stable disease (range 15-34+ wk), and 4 (31%) patients had progressive disease. Four of 7 patients (57%) with baseline CA19-9 > 100 U/mL had a ≥ 70% decrease on study. The median PFS was 5.3 mo and the 6-mo survival rate was 76.2% (42.7%-91.7%)[65]. A randomized phase Ⅱ trial of 10 mg/kg AMG 655 every 2 wk plus Gem has been completed in patients with metastatic pancreatic cancer and the results are forthcoming.

SECOND-LINE CHEMOTHERAPY FOR ADVANCED PANCREATIC CANCER

There is no standard second-line regimen for advanced pancreatic cancer after Gem failure and there is a paucity of trials in this setting. Gem may offer palliative benefits in the second-line setting in patients that have not been treated with Gem previously[66], and results from a phase Ⅱ study (n = 30) suggest that FDR Gem and Ox may have activity in patients who become refractory to standard Gem therapy[67]. All patients received at least one cycle of GemOx (median 5). Response in 31 evaluable patients was as follows: Partial response: 7/31 (22.6%), ≥ 8 wk: 11/31 (35.5%), s.d. < 8 wk: 1/31 (3.2%), Progressive disease: 12/31 (38.7%). Median duration of response and TTP were 4.5 and 4.2 mo, respectively. Median survival was 6 mo (range 0.5-21 mo). The CONKO-3 study[68] randomized 168 patients who had Gem-refractory pancreatic cancer to 5-FU, LV and oxaliplatin (OFF) or 5-FU and LV (FF). The study showed an improved OS by 2 mo in the OFF arm (4.8 mo *vs* 2.3 mo respectively, P = 0.0077). Both regimens were tolerable, with the exception of higher neuropathy in the OFF arm. There was also a significant prolongation of PFS in the treatment arm (13 wk *vs* 9 wk)[68]. After those significant results, this regimen has been regarded as an appropriate second-line regimen for Gem refractory pancreatic cancer patients.

In a phase Ⅲ study patients with advanced pancreatic cancer who had failed at least one line of chemotherapy were randomized to rubitecan or physicians' choice of treatment[69]. Eighty-five percent of patients in both arms had previously received Gem; 70% and 73% had received FU; 60% and 63% had received both drugs in combination, respectively. The study was unable to show a statistically significant improvement in OS (3.7 mo *vs* 3.1 mo, P = 0.626), and PFS was only marginally improved (1.9 mo *vs* 1.6 mo, P = 0.001).

In a phase Ⅱ trial by Cartwright *et al*[70], 42 patients were treated with oral capecitabine 1250 mg/m^2 administered twice daily in 3-weekly cycles consisting of 2 wk of treatment followed by 1 wk without treatment. Twenty-four percent of patients experienced a significant CBR as evidenced by improvement in pain intensity, analgesic consumption, and/or KPS. Three (7.3%) of the 41 patients with measurable disease had an objective partial response. The median time to objective response was 85 d (range, 47 to 91 d) and duration of response was 208, 260, and 566 d for the three responding patients. One patient with non-measurable but assessable disease had improved residual disease with a positive CBR. For a total of 4 responders among the 42 assessable patients, the OS rate was 9.5%[70]. Of note, the capecitabine dose (1000 mg/m^2 *po* twice daily) recommended in the guidelines was less than the dose described by Cartwright *et al*[70], because the higher dose has been associated with increased toxicity (diarrhea, hand and foot syndrome).

In another phase Ⅱ trial[71], pancreatic cancer patients were administered capecitabine (1000 mg/m^2 twice daily for 14 d) combined with Ox (130 mg/m^2 given on day 1 for 14 d) every 21 d (patients aged > 65 years or with an ECOG PS of 2 received Ox 110 mg/m^2 on day 1 and capecitabine 750 mg/m^2 twice daily for 14 d). The treatment was repeated every 3 wk. Of the 39 evaluable patients, 1 patient had a partial response and 10 patients demonstrated stable disease. The median OS was 23 wk and PFS was 9.9 wk. The 6-mo and 1-year survival rates were 44% and 21%, respectively. The most common grade 3-4 non-hematologic toxicity was fatigue[71].

Currently, it is recommended that physicians enroll their patients in a clinical trial if they progress on first-line therapy; however, when investigational therapy is not available, alternatives for good PS patients include capecitabine with or without Ox or OFF.

CONCLUSION

In the first-line setting, Gem with or without erlotinib has been the standard treatment for pancreatic cancer since 1997, despite low response rates and short survival outcome. The recent introduction of targeted therapies in the therapeutic armamentarium against cancer raised hopes in the treatment of patients with advanced or metastatic cancers. Unfortunately, the target agents studied to date have fallen short of these expectations. Knowledge of the molecular events occurring in the malignant transformation processes should allow the development of more efficient targeted therapies. Metastatic and locally advanced pancreatic cancers have consistently been observed as independent predictors of outcome in randomized clinical trials. One should study these two different pancreatic cancer populations separately.

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