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Review

Systemic treatment for inoperable pancreatic adenocarcinoma: review and update

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Abstract

There have been many clinical trials conducted to evaluate novel systemic regimens for unresectable pancreatic cancer. However, most of the trial results were negative, and gemcitabine monotherapy has remained the standard systemic treatment for years. A number of molecular targeted agents, including those against epidermal growth factor receptor and vascular endothelial growth factor receptors, have also been tested. In recent years, there have been some breakthroughs in the deadlock: three regimens, namely gemcitabine-erlotinib, FOLFIRINOX, and gemcitabine-nab-paclitaxel, have been shown to prolong the overall survival of patients when compared with gemcitabine monotherapy. In addition, emerging data suggested that the membrane protein human equilibrative nucleotide transporter 1 is a potential biomarker with which to predict the efficacy of gemcitabine. Here we review the literature on the development of systemic agents for pancreatic cancer, discuss the current choices of treatment, and provide future directions on the development of novel agents.

Key words Pancreatic cancer, chemotherapy, biologics, review, literature

Pancreatic ductal adenocarcinoma (pancreatic cancer) is both a prevalent and aggressive malignancy. The cancer ranks as the eighth and ninth leading global cause of cancer-related death in men and women, respectively[1]. In the Asia-Pacific region, the age-standardized incidence reached a plateau after 1985; yet, the incidence continues to rise due to the aging population in the region[2]. For treatment, surgical resection remains the only curative therapeutic modality for early-stage pancreatic cancer. Despite improvements in surgical technique and patient selection as well as the availability of adjuvant chemotherapy, the 5-year survival rate remains low, ranging from 10% to 20%, following curative resection[3-5]. In addition, because of early asymptomatic disease course and delayed presentation, only approximately 20% of patients are amenable to surgery at diagnosis.

Inoperable pancreatic cancer is composed of heterogeneous populations, namely locally advanced and metastatic disease. The prognosis of the two groups was different: the median survival of patients with untreated locally advanced disease was approximately 8 months, whereas untreated patients with metastatic disease had a median survival of 3 to 4 months only[3]. Despite some controversies about the role of radiotherapy or chemoradiotherapy in patients with locally advanced disease, systemic therapy is the most frequently used treatment modality for inoperable pancreatic cancer. For the past 15 years, there have been a large number of clinical trials conducted to test different systemic therapy regimens for inoperable pancreatic cancer. The goal of this paper is to provide an update on the key randomized clinical trial data on systemic agents for inoperable pancreatic cancer. The future directions of development of systemic agents are also discussed.

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Gemcitabine Monotherapy

Gemcitabine is a pyrimidine anti-metabolite[6] that exerts a wide spectrum of anti-neoplastic effects on different tumor types. Gemcitabine has conventionally been considered the standard regimen for advanced pancreatic cancer on the basis of the phase III clinical trial reported by Burris *et al*.[7]. In the study, 126 patients with advanced pancreatic cancer were randomized to receive either gemcitabine, 1,000 mg/m^2 weekly for 7 courses, followed by 1 week of rest, then days 1, 8, and 15 every 4 weeks, or 5-fluoruracil (5-FU) at the dose 600 mg/m^2 once weekly. The primary endpoint was clinical benefit rate, which was defined as the improvement in disease-related symptoms including pain, performance status, and weight. The final results showed that patients in the gemcitabine arm

had higher clinical benefit rate than did those in the 5-FU arm (23.8% vs. 4.8%, P = 0.002). There was also a modest improvement in the median overall survival (5.6 months vs. 4.4 months, P = 0.002).

Fixed Dose Rate Infusion of Gemcitabine

It has been previously postulated that a longer infusion of gemcitabine is associated with a pharmacokinetic advantage[8]. Therefore, the approach of fixed dose rate infusion, involving the administration of gemcitabine at a fixed rate over a prolonged period of time, has been studied in the clinical trial setting. Despite the initially encouraging data from a phase II clinical trial[9], a phase III intergroup trial from the United States compared the short infusion of gemcitabine with a fixed dose rate (1,500 mg/m^2 over 150 min weekly for 3 of every 4 weeks). The results showed that the fixed dose was not associated with any remarkable benefit in overall survival when compared with the standard infusion of gemcitabine (6.2 months vs. 4.9 months, P = 0.05)[10]. Therefore, the practice of using a fixed dose rate of gemcitabine has been abandoned by most centers globally.

Gemcitabine-Based Combinational Chemotherapy

Following the landmark study by Burris *et al*.[7], single-agent gemcitabine has been considered the standard regimen and used as the backbone for addition of novel chemotherapeutic agents for treatment of inoperable pancreatic cancer. Over the past 15 years, more than 10 chemotherapeutic agents have been tested in combination with gemcitabine versus single-agent gemcitabine in randomized clinical trials. The results are summarized in **Table 1**, and the key details are described as below.

5-FU and its derivatives

5-FU has been tested in combination with gemcitabine among patients with locally advanced or metastatic pancreatic cancer in a phase III clinical trial (E2297 trial)[11]. The dose of 5-FU given in the clinical trial was 600 mg/m^2 per week. Although there was a modest improvement in progression-free survival in the combination of gemcitabine and 5-FU arm (3.4 months vs. 2.2 months, P = 0.022), the median overall survival was not different between the two arms (combination arm, 6.7 months vs. gemcitabine arm, 5.4 months; P = 0.09).

Capecitabine is a prodrug of 5-FU that undergoes three enzymatic steps to form active 5-FU preferentially in tumor tissues. Two phase III clinical trials have been conducted to test the effects of capecitabine combined with gemcitabine (CapGem). In 2007, Herrmann *et al*.[12] reported a phase III clinical trial on CapGem for advanced pancreatic cancer. In the clinical trial, patients in the CapGem arm were treated with gemcitabine at the dose 1,000 mg/m^2 on days 1 and 8, together with capecitabine at the dose 650 mg/m^2 twice daily from day 1 to day 14 every 3 weeks, whereas the patients in the control gemcitabine arm were treated with gemcitabine at the dose similar to the landmark study by Burris *et al*.[7]. The proportion of patients with metastatic disease was approximately 80% in each arm. There was no reported significant difference in overall survival between the two groups (CapGem arm, 7.2 months vs. gemcitabine arm, 8.4 months; P = 0.2). In 2009, Cunningham *et al*.[13] reported another phase III clinical trial on CapGem therapy in a larger number of patients. A total of 533 patients have been randomized to the CapGem arm or the gemcitabine arm, and 70% of these patients have metastatic disease. Although this study adopted a high-dose regimen of capecitabine (830 mg/m^2 oral twice daily from day 1 to day 21 every 4 weeks), there was no survival benefit conferred by the addition of capecitabine to the gemcitabine backbone (CapGem arm, 7.1 months vs. gemcitabine arm, 6.2 months; P = 0.08).

S1 is another oral 5-FU derivative, which includes three different agents: ftorafu, gimeracil, and oteracil. S1 is designed to improve the efficacy of 5-FU by adding 5-FU modulators while limiting 5-FU gastrointestinal toxicities[14]. The combination of S1 and gemcitabine has recently been evaluated in the phase III GEST trial[15]. In the trial, patients with locally advanced or metastatic pancreatic cancer were randomized to S1 (80–120 mg daily from days 1 to 28, every 6 weeks), gemcitabine plus S1 (S1 at 80–120 mg and gemcitabine at 1,000 mg/m^2 on days 1 and 8, every 3 weeks) or gemcitabine monotherapy (1,000 mg/m^2 on days 1, 8 and 15, every 4 weeks). A total of 834 patients have been enrolled. The overall survival of patients in the S1 arm was not inferior to that of patients in the gemcitabine monotherapy arm (S1 arm, 9.7 months vs. gemcitabine arm, 8.8 months; P < 0.001 for non-inferiority). Nevertheless, the combination of S1 and gemcitabine was not superior to gemcitabine monotherapy (S1 plus gemcitabine, 10.1 months vs. gemcitabine, 8.8 months; P = 0.15).

Platinum and its derivatives

Cisplatin is a platinum-based compound that inhibits DNA synthesis by forming platinum-DNA adjuncts[16]. There have been a total of four randomized clinical trials conducted to test the combination of cisplatin and gemcitabine (GemCis), namely studies reported by Colucci *et al*.[17] in 2010, Heinemann *et al*.[18] in 2006, Colucci *et al*.[19] in 2002, and Wang *et al*.[20] in 2002. The most recent study by Colucci *et al*.[17] recruited the largest number of participants (n = 400), which randomized patients with unresectable pancreatic cancer to receive gemcitabine alone or GemCis. The results showed that GemCis did not prolong the median overall survival (GemCis, 7.2 months vs. gemcitabine, 8.3 months; P = 0.38) despite a modest improvement in response rate (GemCis, 12.9% vs. gemcitabine, 10.1%; P = 0.037). The other three clinical studies, with similar design but with smaller sample sizes, also failed to demonstrate an improvement in the overall survival of patients treated with the GemCis regimen, compared with gemcitabine alone[18-20].

Oxaliplatin is a platinum derivative that, like cisplatin, blocks DNA synthesis[21]. There have been two phase III trials to study the combination of oxiliplatin with gemcitabine. Louvet *et al*.[22] recruited 313 patients with stage IV pancreatic cancer and randomized them to receive treatment with gemcitabine-oxaliplatin combination

Table 1. Summary on phase III clinical trials on patients with unresectable pancreatic cancer

Authors and reference	Year of publication	Agent(s)	Arm	No. of patients	Percentage of patients (%)		Response rate (%)	Median overall survival (months)
					Locally advanced pancreatic cancer	Metastatic pancreatic cancer		
Berlin *et al*.[11]	2002	5-FU	GEM + 5-FU	160	10.6	89.4	6.9	6.7
			GEM	162	9.9	90.1	5.6	5.4
Herrmann *et al*.[12]	2007	Capecitabine	GEM + capecitabine	160	20.0	80.0	10.0	8.4
			GEM	159	21.0	79.0	7.8	7.2
Cunningham *et al*.[13]	2009	Capecitabine	GEM + capecitabine	267	30.0	70.0	19.1	6.2
			GEM	266	29.0	71.0	12.4	6.0
Colucci *et al*.[17]	2010	Cisplatin	GEM + cisplatin	201	12.4 [a]	84.6	12.9	7.2
			GEM	199	12.1 [a]	82.9	10.1	8.3
Heinemann *et al*.[18]	2006	Cisplatin	GEM + cisplatin	98	20.0	80.0	10.2	7.5
			GEM	97	21.1	78.9	8.2	6.0
Colucci *et al*.[19]	2002	Cisplatin	GEM + cisplatin	54	19.0 [a]	62.0	26.4	7.0
			GEM	53	26.0 [a]	52.0	9.2	4.7
Wang *et al*.[20]	2002	Cisplatin	GEM + cisplatin	22	18.0 [a]	68.0	11.1	7.2
			GEM	20	20.0 [a]	50.0	6.3	9.1
Louvet *et al*.[22]	2005	Oxaliplatin	GEM + oxaliplatin	157	30.0	70.0	26.8	8.8
			GEM	156	32.0	68.0	17.3	6.9
Poplin *et al*.[10]	2009	Oxaliplatin	GEM + oxaliplatin	272	10.7	89.3	9.0	5.7
			GEM FDR	277	10.2	88.8	10.0	6.2
			GEM	275	9.8	90.2	6.0	4.9
Stathopoulos *et al*.[26]	2006	Irinotecan	GEM + irinotecan	60	22.0	78.0	15.0	6.4
			GEM	70	14.0	86.0	10	6.5
Rocha Lima *et al*.[52]	2004	Irinotecan	GEM + irinotecan	180	15.0 [b]	82.2	16.1	6.3
			GEM	180	13.3 [b]	80.6	4.4	6.6
Abou-Alfa *et al*.[27]	2006	Exatecan	GEM + exatecan	175	21.0	79.0	6.9	6.7
			GEM	174	22.0	78.0	5.2	6.2
Oettle *et al*.[28]	2005	Pemetrexed	GEM + pemetrexed	283	9.9 [c]	90.1	14.0	6.2
			GEM	282	8.9 [c]	91.1	7.1	6.3
Dahan *et al*.[53]	2010	Leucovorin + 5-FU+cisplatin (LV5U2-CDDP)	LV5FU2-CDDP then GEM	102	0	100	19.0	6.7
			GEM then LV5FU2-CDDP	100	0	100	22.0	8.0
Cantore *et al*.[54]	2003	5-FU + leucovorin + epirubicin + carboplatin	5-FU + leucovorin + epirubicin + carboplatin	71	49.2	50.7	14.0	7.9
			GEM	67	47.4	52.2	5.9	5.9
Reni *et al*.[55]	2005	Cisplatin + epirubicin + 5-FU + GEM	Cisplatin + Epirubicin + 5-FU + GEM	52	28.9	81.1	38.5	9
			GEM	47	29.8	70.2	8.5	9
Conroy *et al*.[30]	2011	FOLFIRINOX	FOLFIRINOX	171	0	100	31.6	11.1
			GEM	171	0	100	9.4	6.8
Von Hoff *et al*.[25]	2013	Nab-paclitaxel	GEM + nab-paclitaxel	431	0	100	23.0	8.5
			GEM	430	0	100	7.0	6.7

[a]Remaining belongs to stage II. [b]Remaining stage is unknown. [c]The given value includes stage III and lower disease. 5–FU, fluorouracil; GEM, gemcitabine; FDR, fixed dose rate.

(GemOx) or single-agent gemcitabine. The GemOx regimen includes gemcitabine at 1,000 mg/m^2 on day 1 with oxaliplatin at 100 mg/m^2 infused over 120 min on day 2 every 2 weeks. The study demonstrated an improved objective response rate favoring the GemOx combination (GemOx, 26.8% vs. gemcitabine, 7.3%; P = 0.04), but the primary endpoint, median overall survival, was not different between the two arms (GemOx, 9.0 months vs. gemcitabine, 7.1 months; P = 0.13). Another phase III clinical trial conducted by Poplin *et al*.[10] compared the efficacy of three regimens: GemOx, fixed dose rate infusion of gemcitabine (discussed in section below), and single-agent gemcitabine. No differences in the overall survival or response rates were noted among the arms.

Taxanes

Paclitaxel is an antimitotic agent that binds to tubulin and causes the development of nonfunctional microtubules. Nanoparticle albumin bound (nab)-paclitaxel is prepared by high-pressure homogenization of paclitaxel in the presence of serum albumin into a nanoparticle colloidal suspension. Nab-paclitaxel has several advantages over paclitaxel[23]. First, the infusion duration is 30 min, which is shorter than the 3-hour infusion time of paclitaxel. Second, there is no need for premedications for hypersensitivity reactions. Third, endogenous albumin transport mechanisms may help nab-paclitaxel to become concentrated in the tumor. Following encouraging phase I/II clinical trial results[24], the combination of gemcitabine and nab-paclitaxel has been compared with gemcitabine in phase III settings. The Metastatic Pancreatic Adenocarcinoma Clinical Trial (MPACT) was a multinational phase III trial of 861 patients with previously untreated metastatic pancreatic cancer. Subjects were randomized to undergo treatment with nab-paclitaxel at 125 mg/m^2 followed by gemcitabine at 1,000 mg/m^2 on days 1, 8, and 15 every 4 weeks, or to be treated with gemcitabine at 1,000 mg/m^2 once weekly for 7 weeks and then on days 1, 8, and 15 every 4 weeks. The primary endpoint of the study was overall survival. The final results of the study showed that the median overall survival was better in the combination arm than in the single-agent arm (8.5 months vs. 6.7 months, P < 0.001) and that the response rate was also higher in the combination arm (23% vs. 7%, P < 0.001)[25]. Although the rate of life-threatening toxicities was not increased in the combination arm, grade 3 or 4 adverse events were more frequently observed in the combination arm with regard to neutropenia (38% vs. 27%), fatigue (17% vs. 7%), peripheral neuropathy (17% vs. <1%), and diarrhea (6% vs. 1%)[25].

Other chemotherapeutic agents

Other chemotherapeutic agents such as exatecan, irinotecan, and premetrexed have been tested in phase III settings to determine if the combination of them with gemcitabine provides extra benefit to patients with unresectable pancreatic cancer[26-28]. All of these studies predominantly recruited patients with metastatic disease, including a small proportion with locally advanced disease, and used overall survival as the primary endpoint. No survival benefits have been reported with the addition of a chemotherapeutic agent to gemcitabine treatment.

Meta-analyses of clinical trials studying gemcitabine combination treatment

Due to inconclusive results on the benefits of gemcitabine combination therapy in multiple clinical trials, a number of meta-analyses have been conducted to compare the efficacy of gemcitabine combination versus gemcitabine alone (**Table 2**). Collectively, these analyses show that the gemcitabine combination was associated with a modest benefit in overall survival, with a hazard ratio of 0.9 to 1. Notably, these meta-analyses were conducted before the recent positive data on the gemcitabine-nab-paclitaxel combination became available.

Non-Gemcitabine Chemotherapy

A number of regimens not based on gemcitabine have been tested clinically. Among these non-gemcitabine regimens, the most notable is the FOLFIRINOX regimen developed by a French group. In 2005, Conroy *et al*.[29] reported an intensive regimen involving 5-FU, leucovorin, oxaliplatin, and irinotecan (FOLFIRINOX), which had a promising radiologic response rate of up to 39% in a randomized phase II trial as compared with gemcitabine alone. As a result, the phase II trial was expanded to a phase III clinical trial (ACCORD-11), which randomized patients with chemotherapy-naïve, metastatic pancreatic cancer to FOLFIRINOX or gemcitabine arm. The primary endpoint was overall survival. The target accrual was 342 patients but the clinical trial was stopped after enrolling 250 patients because a preplanned interim analysis showed that the overall survival was significantly longer in the FOLFIRINOX arm (11.1 months vs. 6.8 months, HR = 0.57, P < 0.001)[30]. The FOLFIRNIOX regimen was associated with better response rate (32% vs. 9%, P < 0.001) and better median progression-free survival (6.4 months vs. 3.3 months, P < 0.001) compared with gemcitabine alone. Nevertheless, the improved efficacy of the intensive FOLFIRINOX regimen was at a cost of increased toxicity. Hematologic toxicities, such as neutropenia (45.7% vs. 21.0%, P < 0.001), febrile neutropenia (5.4% vs. 1.2%, P = 0.03), and thrombocytopenia (9.1% vs. 3.6%, P = 0.04), were more noticeable in the FOLFIRINOX arm than in the gemcitabine alone arm. Also, other toxicities including diarrhea (12.7% vs. 1.8%, P < 0.001) and sensory neuropathy (9.0% vs. 0.0%, P < 0.001) were more common in the FOLFIRINOX arm than in the gemcitabine alone arm. The authors concluded that FOLFIRINOX is preferable to gemcitabine in patients with metastatic pancreatic cancer, age younger than 76 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, normal or nearly normal bilirubin level, and no history of cardiac ischemia.

Molecular Targeted Agents

Although a number of targeted agents have been tested for treatment of pancreatic cancer, most did not demonstrate promising activity to proceed to advanced clinical trial testing (**Table 3**). At

Table 2. Summary of meta-analyses on gemcitabine versus its combinations on overall survival of patients with advanced stage pancreatic cancer

Authors and reference	Year of publication	No. of patients	Arm	Overall survival	
				HR/RR/OR (95% CI)	*P*
Sun *et al*.[56]	2012	26	GEM combination vs. GEM	0.90 (0.82–0.99)	0.040
			GEM + fluoropyrimidine vs. GEM	0.95 (0.77–1.16)	0.610
			GEM + camptothecin vs. GEM	0.97 (0.76–1.25)	0.840
			GEM + targeted therapy vs. GEM	0.85 (0.73–1.00)	0.050
			GEM + platinum vs. GEM	0.91 (0.77–1.09)	0.300
Ciliberto *et al*.[57]	2013	34	GEM comination vs. GEM	0.93 (0.85–0.97)	0.001
			GEM + fluropyrimidines vs. GEM	0.91 (0.84–0.99)	0.455
			GEM +others (GEM+PEM, PEGF) vs. GEM	0.87 (0.63–1.22)	0.160
			GEM + platinum vs. GEM	0.91 (0.82–1.01)	0.985
			GEM + biotherapy vs. GEM	0.94 (0.87–1.01)	0.534
			GEM + irinotecan vs. GEM	1.01 (0.83–1.22)	0.687
Eltawil *et al*.[58]	2012	7	GEM + molecular targeted agents vs. GEM	0.94 (0.87–1.01)	0.090
Hu *et al*.[59]	2011	35	GEM vs. GEMCom	1.15	0.011
			GEM vs. GEM + fluoropyrimidine	1.331 (1.081–1.638)	0.007
			GEM vs. GEM + platinum	1.162 (0.981–1.376)	0.082
			GEM vs. GEM + oxaliplatin	1.330 (1.049–1.686)	0.019
			GEM vs. GEM + cisplatin	1.011 (0.794–1.287)	0.928
			GEM vs. GEM + campotothecin	1.029 (0.805–1.315)	0.822
Xie *et al*.[60]	2010	18	GEM + capecitabine vs. GEM	0.85	0.04
			GEM + cisplatin vs. GEM	0.99	0.88
			GEM + 5-FU vs. GEM	0.95	0.46
			GEM + irinotecan vs. GEM	1.03	0.77
			GEM + oxaliplatin vs. GEM	0.80	0.001
Heinemann *et al*.[61]	2008	15	GEM combination vs. GEM	0.91 (0.85–0.97)	0.004
			GEM + platinum-based vs. GEM	0.85 (0.76–0.96)	0.010
			GEM + fluropyrimidine vs. GEM	0.90 (0.81–0.99)	0.030
			GEM + irinotecan/exatecan/pemetrexe vs. GEM	0.99 (0.88–1.10)	NS
Banu *et al*.[62]	2007	23	GEM combination vs. GEM	0.96	0.003
Bria *et al*.[63]	2007	20	GEM combination vs. GEM	0.93	0.170
			GEM + platinum vs. GEM	0.83	0.100
Sultana *et al*.[64]	2007	51	GEM vs. 5-FU	0.75 (0.42–1.31)	0.310
			GEM combination vs. GEM	0.91 (0.85–0.97)	0.004
			GEM + platinum vs. GEM	0.85 (0.74–0.96)	0.010
			GEM + capecitabine vs. GEM	0.83 (0.72–0.96)	0.010
			GEM + irinotecan vs. GEM	1.01 (0.84–1.22)	NS
			GEM + 5-FU vs. GEM	0.98 (0.86–1.11)	0.730
Cunningham *et al*.[13]	2009	3	GEM + capecitabine vs. GEM	0.86 (0.75–0.98)	0.020

GEM, gemcitabine; HR/RR/OR, hazard ratio/relative risk/odds ratio; NS, not significant; vs., versus; PEM, pemetrexed; PEGF, gemcitabine plus 5-fluorouracil, cisplatin and epirubicin.

present, targeted therapy against epidermal growth factor receptor (EGFR) is the only class of molecular targeted agents tested in the phase III setting. EGFR is overexpressed and implicated in the progression of pancreatic cancer, supporting the therapeutic use of agents targeting EGFR[31-33]. Two anti-EGFR agents, namely erlotinib and cetuximab, have been tested. Erlotinib, a tyrosine kinase inhibitor against EGFR, was tested in combination with gemcitabine in a phase III clinical trial from the National Cancer Institute of Canada[34]. In the study, a total of 569 patients with locally advanced or metastatic pancreatic cancers were randomly assigned to undergo gemcitabine with erlotinib therapy at a dose of 100 mg or 150 mg per day, or gemcitabine and placebo therapy[34]. Although there was no difference in the objective response rate between the two arms, the combination of gemcitabine and erlotinib was associated with a statistically significant improvement in the overall survival (6.2 months vs. 5.9 months, $P = 0.038$). Regarding the toxicity, this combination was associated with more grade 3 or above toxicities especially diarrhea and skin rash. This clinical trial

Table 3. Summary of clinical studies on targeted agents for treatment of pancreatic cancer

Authors and reference	Year of publication	Agent	Arm	Phase	No. of patients	Percentage of patients (%)		Response rate (%)	Median overall survival (months)
						Locally advanced pancreatic cancer	Metastatic pancreatic cancer		
Small molecule									
Moore *et al*.[65]	2003	MMP inhibitor	BAY 12-9566	III	138	38[a]	62	1	3.7
			vs. GEM		139	35[a]	65	5	6.6
Van Cutsem *et al*.[66]	2004	Farnesyltransferase inhibitor	GEM + tipifarnib	III	341	NA	NA	6	6.2
			vs. GEM + placebo		347	NA	NA	8	5.9
Senderowicz *et al*.[67]	2007	EGFR	GEM + erlotinib	III	261	23	77	8.6	6.5
			vs. GEM + placebo		260	24	76	7.9	6.0
Moore *et al*.[34]	2007	EGFR	GEM + erlotinib	III	285	23.5	76.5	8.6	6.2
			vs. GEM + placebo		284	25	75	8	5.9
Kindler *et al*.[39]	2011	VEGFR	GEM + axitinib	III	314	25[b]	72	5	8.5
			vs. GEM + placebo		316	23[b]	72	2	8.3
Monoclonal antibody									
Philip *et al*.[36]	2010	EGFR	GEM + Cetuximab	III	372	21	79	12	6.3
			vs. GEM		371	22	78	14	5.9
Kullmann *et al*.[37]	2009	EGFR	Cetuximab + GEM/oxaliplatin	II	61	0	100	33	6.9
Kindler *et al*.[68]	2010	VEGF-A	GEM + bevacizumab	III	302	16	84	13	5.8
			vs. GEM + placebo		300	15	85	10	5.9
Combination of small molecule and monoclonal antibody									
Van Cutsem *et al*.[40]	2009	VEGF-A	GEM + erlotinib + bevacizumab	III	306	0	100	13.5	7.1
			vs. GEM + erlotinib		301	0	100	8.6	6.0
Ko *et al*.[69]	2010	VEGF and EGFR	Bevacizumab + erlotinib	II	36	0	100	2.8	3.4

[a]The given number includes stage III and lower disease. [b]Remaining belongs to stage II. EGFR, epidermal growth factor receptor; GEM, gemcitabine; MMP, matrix metalloproteinase; NA, not available; VEGF(R), vascular endothelial growth factor (receptor).

led to the US Food and Drug Administration's approval in 2005 of the combination of gemcitabine and erlotinib as a systemic regimen for patients with inoperable pancreatic cancer. On the other hand, cetuximab is a chimeric monoclonal antibody that acts against EGFR on the cellular membrane. The antitumor activity of gemcitabine and cetuximab was initially observed in a phase II trial[35], which led to the commencement of a multicenter phase III clinical trial comparing the gemcitabine-cetuximab regimen with gemcitabine alone[36]. Disappointingly, the combination regimen did not improve the response rate or the overall survival. Other randomized phase II trials failed to demonstrate survival benefit from the combination of cetuximab and chemotherapy[37,38].

Similar to the anti-EGFR approach, the antiangiogenic approach did not appear effective against advanced pancreatic cancer. For example, the antiangiogenic small-molecule axitinib, which targets vascular endothelial growth factor (VEGF) receptor, has been tested in combination with gemcitabine in a randomized phase II clinical trial, but the combination did not demonstrate an improvement in overall survival[39]. Bevacizumab, a monoclonal antibody against VEGF, has been tested in combination with gemcitabine-erlotinib doublet in a phase III clinical trial[40]. In the study, 607 patients were randomly assigned to gemcitabine-erlotinib with or without bevacizumab arm. The addition of bevacizumab did not improve the overall survival (bevacizumab, 7.1 months vs. placebo, 6 months; $P = 0.21$)[40].

Second-Line Treatment

There have been few randomized studies to determine the benefits of second-line therapy. For patients who have been treated previously with gemcitabine as first-line therapy, a randomized trial has assigned patients to receive either FOLFOX, which is a regimen composed of oxaliplatin, 5-FU and folinic acid, or best supportive care alone[41]. However, the trial was stopped prematurely because of poor accrual. Based on 46 patients recruited in the study, there was

an improvement in the overall survival favoring second-line FOLFOX (4.8 months vs. 2.3 months, P = 0.008)[41]. Other case series or phase II trials have also indicated potential clinical benefit for second-line chemotherapy following disease progression with first-line gemcitabine[42-44]. On the other hand, for patients who were treated with FOLFIRINOX as the first-line therapy, there were no data on the optimal second-line regimen, but gemcitabine monotherapy appeared to be a reasonable option in view of its relatively good tolerance.

Systemic Therapy for Inoperable Pancreatic Cancer: Status in 2013

Despite tremendous effort, a large number of clinical trials failed to demonstrate additional survival benefit in using systemic therapy compared with gemcitabine alone. At present, three novel regimens have succeeded in improving the clinical outcomes and prolonging the overall survival of patients with inoperable pancreatic cancer: the gemcitabine-erlotinib combination[34], FOLFIRINOX[30], and the gemcitabine-nab-paclitaxel regimen[25]. Although gemcitabine-erlotinib was associated with a survival benefit in a phase III clinical trial when compared with gemcitabine alone, most clinicians consider the less than 1 month improvement in overall survival too short to be clinically meaningful. In fact, subsequent clinical trials using the gemcitabine-erlotinib doublet as the backbone failed to demonstrate impressive overall survival improvement[40]. Together with the negative results of cetuximab, it remains unclear whether the combination of anti-EGFR treatment and chemotherapy could improve the outcome of pancreatic cancer.

Based on the presented data, FOLFIRINOX was likely the most effective regimen for treatment of inoperable pancreatic cancer. The ACCORD-11 phase III clinical trial was built on the promising results of the phase II trial. The antitumor activity was evidenced by not only a significant improvement in overall survival but also the improved radiologic response rate and progression-free survival. One limitation of the study is its generalizability. More specifically, the trial population was relatively young and fit, with a median age of 61 years, ECOG performance status of 0 or 1, and an absence of jaundice. Although the clinical trial has demonstrated reasonable and manageable toxicity in this population, the toxicity is likely to be more significant and prevalent in patients with less optimal health conditions. Indeed, in real-world practice, FOLFIRINOX is frequently modified to a less aggressive regimen, such as by omitting bolus 5-FU or reducing the dose of oxaliplatin and irinotecan.

The MPACT data in 2013 supported gemcitabine-nab-paclitaxel as another option[25]. As compared with gemcitabine alone, the regimen is associated with consistent benefit in overall survival, response rate, and progression-free survival. Currently, there is no head-to-head comparison of gemcitabine-nab-paclitaxel and FOLFIRINOX, but cross-trial comparison suggested that gemcitabine-nab-paclitaxel was likely a better tolerated regimen. In addition, the MPACT has recruited a small proportion of patients over the age of 75 years or with Karnofsky performance status $\geqslant$ 70, further suggesting that the regimen might be better tolerated than the FOLFIRINOX.

Development of Systemic Therapy: Future Directions

Development of novel agents

After decades of developing cytotoxic agents, it has become evident that the benefit of chemotherapy has reached a plateau. Although gemcitabine is well tolerated, it does not appear to be a good backbone for combination with other chemotherapeutic or molecular-targeted agents. On the other hand, FOLFIRINOX is associated with better antitumor efficacy, but its toxicity profile also renders the regimen difficult to further combine with other cytotoxic chemotherapy. Similar to other solid tumors, further breakthroughs will likely rely on development of targeted agents for the disease[45-47]. Experience from breast and non–small cell lung cancers suggests that success in clinical trials of targeted therapy can only be improved if the agents are applied to carefully selected patients whose tumors are addicted to a known driver gene. Thus, the ideal developmental approach would be to identify key genetic mutations of pancreatic cancer before clinically testing novel agents. To this end, it is important to obtain histologic samples before or along the conduct of clinical trials. Owing to the invasive nature of tumor biopsy, a number of groups are currently studying the use of massive parallel sequencing to study the genome of cancer in plasma samples, which could potentially obviate the need of needle biopsy[48,49].

Predictive biomarkers

Human equilibrative nucleoside transporter 1 (hENT1) is a membrane protein responsible for intracellular transport of gemcitabine. In the adjuvant setting, hENT1 expression in resected tissue is a prognostic marker for overall survival in patients treated with gemcitabine but not in patients treated with 5-FU[50]. Therefore, it has been postulated that the expression of hENT1 could serve as a predictive biomarker for gemcitabine in pancreatic cancer. However, there is currently no data on the role of this marker in predicting tumor response to gemcitabine in patients with inoperable pancreatic cancer. Further studies are required to validate the role of hENT1 in advanced pancreatic cancer before generalized use.

Patient selection

Most of the previous clinical trials on novel agents have recruited patients with either metastatic or locally advanced disease. It has become clear that these two populations have different prognoses and distinct responses to chemotherapy. Recent clinical trials have gradually changed from focusing on patients with unresectable disease to those with only metastatic disease in order to ensure homogeneous phenotypes and prognosis during the testing of novel agents. This is evidenced by strikingly similar overall survival, approximately 6.8 months, in the MPACT and ACCORD-11 trials, which both recruited only patients with metastatic disease[30,51]. Therefore, it is necessary to divide the population of unresectable pancreatic cancer into locally advanced and metastatic disease

during testing of novel agents.

Conclusions

The systemic treatment of advanced pancreatic cancer has evolved from gemcitabine monotherapy to a number of active regimens, especially gemcitabine-nab-paclitaxel and FOFIRINOX. With these advancements, the median overall survival of patients with metastatic pancreatic cancer has improved from 6 months to 11 months. The success on development of novel treatment for pancreatic cancer relies on not only identification of more therapeutic targets but also better patient selection for clinical trials.

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