

WJG 20th Anniversary Special Issues (14): Pancreatic cancer**Optimum chemotherapy in the management of metastatic pancreatic cancer**

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Abstract

Pancreatic cancer is one of the most devastating solid tumors, and it remains one of the most difficult to treat. The treatment of metastatic pancreatic cancer (MPC) is systemic, based on chemotherapy or best supportive care, depending on the performance status of the patient. Two chemotherapeutic regimens have produced substantial benefits in the treatment of MPC: gemcitabine in 1997; and FOLFIRINOX in 2011. FOLFIRINOX improved the natural history of MPC, with overall survival (OS) of 11.1 mo. *Nab*-paclitaxel associated with gemcitabine is a newly approved regimen for MPC, with a median OS of 8.6 mo. Despite multiple trials, this targeted therapy was not efficient in the treatment of MPC. Many new molecules targeting the proliferation and survival pathways, immune response, oncofetal signaling and the epigenetic changes are currently undergoing phase I and II trials for the treatment of MPC, with many promising results.

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Key words: Metastatic pancreatic cancer; Chemotherapy; Evolution; Recent therapies; Targeted therapy

Core tip: This paper will be the newest study with the most recent updates in the treatment of metastatic pancreatic cancer. After a brief review of the different treatments for metastatic pancreatic cancer, the current treatment options are discussed, as well as novel therapies and approaches in the future.

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INTRODUCTION

Pancreatic cancer (PC) is one of the most aggressive and devastating solid tumors with the worst mortality. The median overall survival (OS) is less than 6 mo, and less than five percent of patients will survive more than 5 years (2% in cases of metastatic pancreatic cancer). The large majority of pancreatic cancers are locally advanced (50%) or metastatic (40%) because of their late diagnoses^[1].

PC remains one of the most difficult cancers to treat due to its intrinsic resistance to conventional treatments. Many regimens have been implicated in the treatment of metastatic pancreatic cancers (MPC), but only two have had significant impact: GEMCITABINE, introduced in 1997^[2]; and FOLFIRINOX, introduced in 2011^[3]. In the era of targeted therapy, the treatment of pancreatic cancer remains based mainly on chemotherapeutic regimens.

Table 1 Summary of the results of four trials associating Gemcitabine and targeted therapies

Ref.	Regimen	ORR	Median PFS (mo)	Median OS (mo)
Philip <i>et al</i> ^[10]	Gem/cetuximab	12.5%	3.4	6.3
	Gem	14.0%	3	5.9
Kindler <i>et al</i> ^[11]	Gem/bevacizumab	13.0%	3.8	5.8
	Gem	10.0%	2.9	5.9
Moore <i>et al</i> ^[12]	Gem/erlotinib	8.6%	3.75	6.24
	Gem	8.0%	3.55	5.91
Rougier <i>et al</i> ^[13]	Gem/aflibercept	ND	3.7	6.5
	Gem	ND	3.7	7.8

ORR: Objective response rate; PFS: Progression free survival; OS: Overall survival; ND: Not determined.

EVOLUTION OF TREATMENT MODALITIES

The primary goals of treatment in MPC are better quality of life, palliation and improved survival. The vast majority of chemotherapeutic drugs have been tried in the treatment of MPC, but few have been selected as standards of care.

Before the approval of GEMCITABINE, 5-FU was the most evaluated agent for MPC, without any survival amelioration. In 1997, Gemcitabine was approved by the FDA, based on the results of a randomized trial, in which Gemcitabine was compared to 5-FU in previously untreated patients. A total of 23.8% of Gemcitabine-treated patients experienced a clinical response, compared with 4.8% of 5-FU-treated patients ($P = 0.0022$), while the median survival was only extended by 1.24 mo (5.65 *vs* 4.41) in favor of patients receiving Gemcitabine ($P = 0.025$). The one-year survival rate was 18% for Gemcitabine patients and 2% for 5-FU patients^[2].

Since the Gemcitabine era, many gemcitabine-based combination therapies have been widely evaluated over the past decade. Most trials have used a second cytotoxic agent, such as 5-FU^[4], capecitabine^[5], oxaliplatin^[6], cisplatin^[7], irinotecan^[8] and pemetrexed^[9], or a targeted therapy, such as cetuximab^[10], bevacizumab^[11], erlotinib^[12] and aflibercept^[13], administered in combination with gemcitabine (Table 1). However, despite a modest improvement in progression-free survival in some trials, a significant benefit in overall survival could not be demonstrated for the majority of these combination therapies.

Of all of these treatments, erlotinib, which positively impacted overall survival, was approved for the treatment of metastatic pancreatic cancer^[10]; the addition of bevacizumab to gemcitabine-erlotinib did not lead to a statistically significant improvement in OS^[14]. A trend toward better survival was also observed with a gemcitabine-capecitabine regimen. Finally, two meta-analyses, the first by Heineemann *et al*^[15] and the second by Sultana *et al*^[16], concluded that there was a significant survival benefit when gemcitabine was associated with another agent (platinum and 5-FU derivatives) in patients with good performance status. A recent retrospective study by Khalil *et al*^[17] in 2013

reported that adding erlotinib to gemcitabine-cisplatin did not appear to improve OS in MPC.

In 2007, we reported on a phase II clinical trial assessing a gemcitabine-free regimen based on FOLFOX 6, with promising results. A partial response was observed in 27.5% of the patients and stable disease in 34.5%^[18]. Our study and the study by Louvet *et al*^[6], which associated gemcitabine and oxaliplatin (RR of 26.8%, the highest with any gemcitabine-based regimen), highlighted the potential role of oxaliplatin in the treatment of MPC.

A second revolution marked the history of MPC in 2011, when Conroy *et al*^[3] reported for the first time in NEJM a significant improvement in OS using a gemcitabine-free regimen—the FOLFIRINOX regimen, based on three chemotherapeutic drugs: 5-FU, irinotecan and oxaliplatin. In this study, the median OS of the patients receiving FOLFIRINOX was 11.1 mo compared to 6.8 mo in the group of patients receiving gemcitabine alone, with an objective response rate of 31.6% compared to 9.4% in favor of the FOLFIRINOX arm. However, more adverse events, such as febrile neutropenia, thrombocytopenia, sensory neuropathy and diarrhea, were noted in the group of patients receiving FOLFIRINOX. This regimen was considered an option for the treatment of patients with MPC and good performance status^[3]. A recent study demonstrated that FOLFIRINOX significantly reduced quality of life impairment compared with gemcitabine in patients with MPC^[19].

Since the results with the FOLFIRINOX gemcitabine-free regimen, a new attempt with gemcitabine-based combination therapy revealed promising results. Another agent added to gemcitabine was the *nab*-paclitaxel, an albumin-bound nanoparticle form of paclitaxel that increases the tumor accumulation of paclitaxel through binding of albumin to SPARC. A randomized phase III study that compared a combination of *nab*-paclitaxel and Gemcitabine weekly to gemcitabine alone showed a significant improvement in overall survival of 8.5 mo *vs* 6.7 mo ($P < 0.05$) and a response rate of 23% *vs* 7%^[20]. An important prognostic biomarker in patients with MPC receiving *nab*-paclitaxel is SPARC; a positive SPARC status in these patients was associated with a significant increase in OS^[21].

CURRENT TREATMENT OPTIONS

Treatment is systemic, based on chemotherapy or best supportive care, depending on the performance status of the patient.

In patients with limited performance status, Gemcitabine as monotherapy is the uniquely approved treatment; another alternative is best supportive care. In patients with good performance status, many chemotherapeutic regimens are available (Table 2). Gemcitabine is still considered a possible option^[1]. FOLFIRINOX offers the best overall survival and response rate in MPC, but it causes many side effects. Gemcitabine associated with *nab*-paclitaxel offers the second best overall survival, with fewer side effects compared to FOLFIRINOX^[16,18].

Table 2 The approved chemotherapeutic regimens for metastatic pancreatic cancer in patients with good performance status

Ref.	Regimen	ORR	Median OS (mo)	Median PFS (mo)
Burriss <i>et al</i> ^[21]	Gemcitabine	ND	5.65	2.33
	5-FU	ND	4.41	0.92
Conroy <i>et al</i> ^[23]	FOLFIRINOX	31.6%	11.1	6.4
	Gemcitabine	9.4%	6.8	3.3
Moore <i>et al</i> ^[12]	Gemcitabine/ erlotinib	8.6%	6.24	3.75
	Gemcitabine	8.0%	5.91	3.55
Daniel <i>et al</i> ^[20]	Gemcitabine/ <i>nab</i> -paclitaxel	23%	8.5	5.5
	Gemcitabine	7%	6.7	3.7

ORR: Objective response rate; OS: Overall survival; PFS: Progression free survival; ND: Not determined.

A comparison between the side effects of these three regimens is resumed in the Table 3. Erlotinib remains the unique targeted therapy approved for the treatment of MPC in combination with gemcitabine. Gemcitabine combined with cisplatin or capecitabine can be a reasonable choice in some cases. Patients with MPC and good performance status can also be included in different phase I or II clinical trials. All of the approved treatments for MPC in patients having poor and good performance status are reviewed in Figure 1.

The second-line treatment for MPC has been evaluated in only a few trials. The general guidelines for treatment are to use fluoropyrimidine-based chemotherapy if the patient was previously treated with gemcitabine-based chemotherapy and gemcitabine-based chemotherapy if previously treated with fluoropyrimidine-based therapy^[22]. A phase II trial investigated whether the association of capecitabine with oxaliplatin was active in gemcitabine-pretreated patients with MPC, especially patients with a good performance status and those who responded to first-line chemotherapy^[23]. A phase III trial comparing the OFF regimen (oxaliplatin; 5-FU; folinic acid) to best supportive care provided first-time evidence for the benefit of second-line chemotherapy in MPC, manifested by prolonged survival time^[24]. Palliative radiotherapy has been proposed as salvage therapy for patients with severe pain refractory to narcotics^[22].

Novel therapies and approaches

Epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) have been considered, for the last decade, the two main targets that should be studied in MPC. Many trials have combined gemcitabine with an anti-angiogenic drug or a tyrosine-kinase inhibitor (Table 1); all of these trials have had negative results, except for the combination of gemcitabine and erlotinib, as mentioned above.

After multiple failures with targeted therapy for MPC based on anti-EGFR and anti-VEGF, many new concepts for treating MPC are being elaborated, including the targeting of tyrosine kinase signaling, cascade ele-

Table 3 The adverse events of three approved regimen for metastatic pancreatic cancer reported in NEJM 2011 and ASCO 2013

Adverse events	Gemcitabine	FOLFIRINOX	Gemcitabine/ <i>nab</i> -paclitaxel
Neutropenia	21%	45.7%	38%
Febrile neutropenia	1.2%	5.4%	3%
Thrombocytopenia	3.6%	9.1%	13%
Fatigue	17.8%	23.6%	17%
Diarrhea	1.8%	12.7%	6%
Peripheral neuropathy	0%	9.0%	17%

ments, the stromal reaction, the immune response, oncofetal signaling and epigenetic changes^[25].

IFG1R, MEK, PI3K, AKT, and mTOR are actually the most frequent signaling pathway targets evaluated in the treatment of MPC. A phase II trial reported that ganitumab (AMG 479), an mAb antagonist of insulin-like growth factor 1 receptor, combined with gemcitabine showed a trend toward improved 6-mo survival and overall survival rates^[26]. Many other trials had negative results: selumetinib (AZD6244), a selective MEK inhibitor compared to capecitabine as a second-line treatment after gemcitabine, did not demonstrate any statistically significant difference in overall survival^[27]; an oral m-TOR inhibitor (RAD001) had minimal clinical activity in gemcitabine-resistant MPC^[28].

Immunotherapy is one of the promising new concepts introduced in the treatment of MPC. A phase I study of an agonist of CD40 monoclonal antibody (CP-870, 893), in combination with gemcitabine, was well tolerated in patients with MPC and was associated with anti-tumor activity^[29]. Ipilimumab (anti-CTLA-4), another immunotherapeutic option approved for metastatic melanoma^[30], was considered ineffective in the treatment of MPC after the results of a phase II trial; association of these agents with other agents could probably have more promising results^[31].

Another approach in the treatment of MPC is the targeting of oncofetal signaling, which is responsible for tumor progression and resistance to chemotherapy in PC. One of the most altered pathways incriminated in the development of PC is the Notch pathway^[32]; the activation of γ -secretase is the primum movens of activation of Notch signaling. Preclinical data suggested that a selective γ -secretase inhibitor (PF-03084014) had greater anti-tumor activity in combination with gemcitabine in PC, providing a rationale for further investigation of this combination in PC^[33]. Many other trials are evaluating agents targeting the stromal reaction and epigenetic changes^[34,35].

Another targeted therapy, AGS-1C4D4, a fully human monoclonal antibody against prostate stem cell antigen, was evaluated with gemcitabine in a randomized phase II study of untreated MPC, with achievement of its primary end point in demonstrating improved 6-mo SR^[36]. All of the recent phase II trials studying the new agents in the treatment of MPC are summarized in

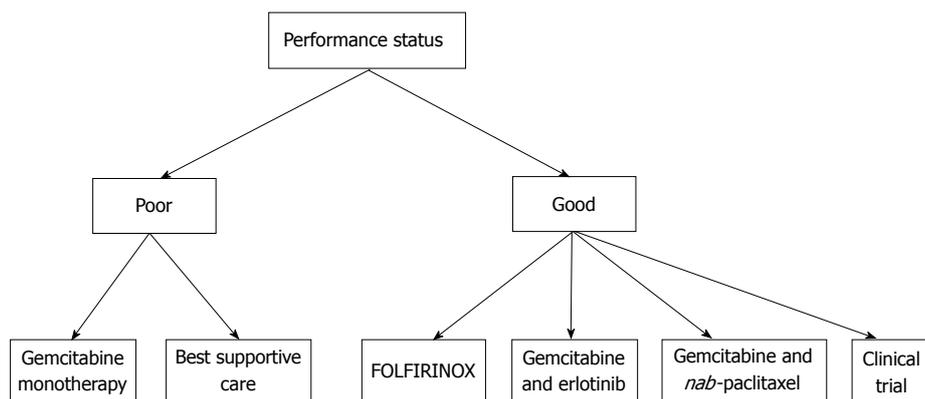


Figure 1 A schema representing the approved treatment for metastatic pancreatic cancer in patients having poor or good performance status.

Table 4 Recent phase II trials studying new agents in the metastatic pancreatic cancer

Reference	New agents	Agents target	Phase of the study and targeted population	Arms of the study	Conclusion of the study
Kindler <i>et al</i> ^[26]	Ganitumab (AMG479)	mAb antagonist of insulin-like growth factor 1 receptor	Phase II; untreated MPC patients	Gem/ganitumab vs gem	Improved 6-mo survival rate and OS
Bodoky <i>et al</i> ^[27]	Selumetinib (AZD6244)	Selective MEK inhibitor	Phase II; second line treatment after gemcitabine	Selumetinib vs capecitabine	No significant difference in OS
Wolpin <i>et al</i> ^[28]	Everolimus (RAD001)	m-TOR inhibitor	Phase II; second line treatment after gemcitabine	Everolimus (single arm study)	Minimal clinical activity
Royal <i>et al</i> ^[31]	Ipilimumab (MDX010)	Anti-CTLA4	Phase II; untreated MPC patients	Ipilimumab (single arm study)	Ineffective in the treatment of MPC
Wolpin <i>et al</i> ^[36]	AGS-1C4D4	mAb to prostate stem cell Antigen	Phase II; untreated MPC patients	Gemcitabine/AGS-1C4D4 vs gemcitabine	Improved 6-mo survival rate

MPC: Metastatic pancreatic cancer; OS: Overall survival.

Table 4.

Many new targets and genes that play roles in the pathogenesis and progression of PC are being evaluated in animals or in cancer cells for their potential diagnostic and therapeutic implications: mucin (myc) was studied by Rachagani *et al*^[37], transketolase by Wang *et al*^[38] and aberrant CD20 expression by Chang *et al*^[39].

The combination of these novel therapies and approaches could positively affect the history of MPC.

CONCLUSION

Despite multiple trials and their major efforts, PC remains resistant to chemotherapy and targeted therapy. It seems that the results obtained with chemotherapy, targeted therapy and their combination in MPC have reached a plateau, with significant, but modest, amelioration of OS of less than one year. Stratified or personalized therapy is totally absent in the treatment of MPC, due to the absence of prognostic or therapeutic markers and the lack of molecular profiling modalities. Many trials are currently being conducted to explore new targets in the tumorigenesis and proliferation of PC. Finally, the combination of these novel therapies with personalized medicine might offer promising results in patients with MPC.

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