

Metastatic pancreatic cancer: Is gemcitabine still the best standard treatment? (Review)

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Abstract. Pancreatic ductal adenocarcinoma is the fourth cause of death in the Western world. Surgery remains the only treatment offering an advantage in terms of overall survival (5-year survival range, 15-25%), but unfortunately only 10-20% of patients present resectable disease at the time of diagnosis. Hence chemotherapy, possibly combined with radiation therapy, remains the only treatment option aimed at palliation of symptoms and ensuring a better quality of life. Notwithstanding the efforts to find more effective therapies for the treatment of pancreatic cancer, significant results have not yet been achieved. Increasing interest has focused on integrated treatments, i.e. chemotherapy combined with targeted therapies, and a better selection of patients. This study examines the principal clinical trials that will help give clinicians an overview of the progress made in the systemic therapy for advanced pancreatic cancer patients in recent years.

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1. Introduction

Pancreatic ductal adenocarcinoma is one of the commonest gastrointestinal tract malignancies and the fourth cause of cancer-related death in the Western world.

The natural history of this tumour is characterized by a poor outcome for all stages of disease and only 1-4% of pancreatic cancer patients are still alive at 5 years from diagnosis (1).

Despite the advances in cancer therapy, the treatment of pancreatic cancer patients remains one of the major challenges of medical oncology. To date, the radical surgical resection of pancreatic ductal adenocarcinoma remains the only treatment offering an advantage in terms of overall survival (5-year survival range, 15-25%). Unfortunately, in most cases, the disease is no longer susceptible to a radical surgery when it is clinically manifested. Hence, only 10-20% of patients present resectable disease at the time of diagnosis (2).

For the majority of patients with pancreatic cancer, chemotherapy, possibly combined with radiotherapy, remains the only treatment option aimed at palliating symptoms and ensuring a better quality of life, without changing the poor prognosis.

Notwithstanding the efforts to find more effective therapies for the treatment of pancreatic cancer, significant results have not yet been achieved. Increasing interest has focused on integrated treatments, i.e. chemotherapy combined with targeted therapy.

The objective of this review is to help clinicians focus on what has been done in systemic palliative therapy for the advanced pancreatic patients in recent years. We examined the principal clinical trials which used cytotoxic chemotherapeutic agents or molecular-targeted therapies or both.

2. From 5-fluorouracil to gemcitabine

5-Fluorouracil (5-FU) was considered the only chemotherapeutic option for about 20 years until the registration of gemcitabine. Several trials showed that chemotherapy leads to an improved survival and quality of life compared to the best supportive care (BSC) in advanced pancreatic cancer patients (3,4), but the combination of 5-FU with other drugs did not prove superior to the antimetabolite alone (5-9) (Table I).

Table I. 5-Fluorouracil based chemotherapy regimens.

Regimen	Refs.	Type of study	No. of patients	Stage disease	Median survival	PFS	1-year survival (%)	RR (%)
FU vs. FU + CDDP	Ducieux <i>et al</i> (7)	III	207	LA/M	102 vs. 112 days (p=0.10)	59 vs. 73 days	8.7 vs. 17.3 (p=0.07)	0 vs. 12 (p=0.01)
FU (PVI) vs. FU (PVI) + mitomycin	Maisey <i>et al</i> (8)	III	209	LA/M	5.1 vs. 6.5 mo (p=0.338)	2.8 vs. 3.8 mo (p=0.14)	23.5 vs. 32.2 (p=0.338)	8.4 vs. 17.6 (p=0.04)
FU vs. OXA vs. OXFU	Ducieux <i>et al</i> (9)	II	65	LA/M	5-FU: 2.4 mo OXA: 3.4 mo OXFU: 9.0 mo	5-FU: 1.5 mo OXA: 2.0 mo OXFU: 4.2 mo	-	OXFU: 10

FU, 5-fluorouracil; CDDP, cisplatin; OXA, oxaliplatin; OXFU, OXA + FU; PVI, protracted venous infusion; LA, locally advanced; M, metastatic; OS, overall survival; PFS, progression-free survival; RR, response rate.

During the 1990s, several trials were designed to find new active drugs in pancreatic cancer treatment and the nucleoside analogous gemcitabine (2'-deoxy-2',2'-difluorocytidine) has aroused considerable interest (10-12). The pivotal trial found a clear improvement of the one-year median survival rate in patients treated with gemcitabine over those who received 5-FU (18 vs. 2%, $p=0.0001$). That study also introduced the concept of clinical benefit response (CBR) that was defined as a $\geq 50\%$ reduction in pain intensity, daily analgesic consumption or ≥ 20 point improvement in Karnofsky performance status (PS) for ≥ 4 consecutive weeks. CBR was significantly improved in gemcitabine treated patients ($p=0.0022$) (13).

Several recent clinical trials proposed different gemcitabine administration schedules. Phase I and II studies showed the effectiveness of the fixed-dose rate regimen (FDR) (14). Based on the fact that anti-cancer drug activity was improved by a prolonged infusion, a randomized phase II trial compared the regimen of 2200 mg/m² with a standard 30-min infusion with a FDR regimen of 1500 mg/m² over 150 min in locally advanced or metastatic pancreatic cancer patients (91%). The FDR regimen resulted in a better OS than the standard regimen ($p=0.013$), but more severe adverse events, namely hematological toxicity, were observed (15). However, a confirmatory phase III trial failed to demonstrate an improvement in OS of gemcitabine FDR regimen over the standard administration (16). In conclusion, the optimal clinical application of gemcitabine FDR remains a matter of lively debate.

3. Gemcitabine-combined regimens

Many phase II studies demonstrated the efficacy of gemcitabine combination treatments, but none of the randomized phase III trials confirmed the improvement in OS of gemcitabine-based doublets compared to gemcitabine alone (14,17). However, an advantage in six-month mortality was given by combining gemcitabine-fluoropyrimidine analogues and gemcitabine-platinum analogues, as demonstrated in the meta-analysis of Heinemann and colleagues

(3,18). Another phase II study confirmed the improved efficacy of the gemcitabine-based combination with better results for patients with a good baseline PS (19). Table II summarizes the randomized phase III trials comparing gemcitabine combination regimens over gemcitabine alone.

Gemcitabine and 5-fluorouracil. Based on the complementary pharmacology of their mechanisms of action, the combination of 5-FU and gemcitabine was evaluated in many phase I and II trials. The interpretation of results suggested a clinical activity of the association schedule with a good tolerability (19-22).

The first important randomized phase III trial evaluated the combination regimen compared to gemcitabine alone. The objective response (OR) and median OS did not differ between the two treatment arms (23). In addition, the Italian Group for Clinical Oncology Research (GOIRC) evaluated the efficacy of gemcitabine in combination with or without continuous 5-FU infusion. This trial also failed to report a significant improvement of median OS (31 vs. 30 weeks) and median progression-free survival (PFS) (14 vs. 18 weeks), in the experimental arm (24).

Gemcitabine and capecitabine. Capecitabine is an orally administered fluorouracil pro-drug, which is activated by a three-step targeted process (carboxylesterases, cytidine deaminase and thymidine phosphorylase respectively). This drug mimics the continuous infusion of 5-FU and its intratumoral activation improved the therapeutic index and reduced toxicity in normal tissue.

Phase I and II trials showed discordant results regarding the efficacy of the gemcitabine-capecitabine combination. These studies used different schedules but none of them were able to demonstrate a certain advantage over gemcitabine alone (25-29).

An abstract of one important phase III trial involving 533 patients reported an improvement in OS ($p=0.014$) and one-year survival in patients who received gemcitabine (1000 mg/m²) on days 1, 8, 15 plus capecitabine (1660 mg/m²/day) on days 1-21 every 28, compared to those who

Regimen	Refs.	Type of study	No. of patients	Stage disease	Median survival (mo)	PFS	1-year survival (%)	RR (%)
GEMFU vs. GEM	Berlin <i>et al</i> (19)	III	327	LA/M	6.7 vs. 5.4 mo (p=0.09)	3.4 vs. 2.2 mo (p=0.022)	-	6.9 vs. 5.6
GEMCAPE vs. GEM	Cunningham <i>et al</i> (30)	III	533	LA/M	7.4 vs. 6 mo	-	26 vs. 19	17 vs. 4 (p=0.008)
GEMCAPE vs. GEM	Herrmann <i>et al</i> (31)	III	319	LA/M	8.4 vs. 7.2 mo (p=0.234)	4.3 vs. 3.9 mo (p=0.103)	32 vs. 30	10 vs. 7.8
GEMCIS vs. GEM	Colucci <i>et al</i> (47)	III	107	LA/M	7.5 vs. 5 mo (p=0.43)	4.6 vs. 1.8 mo (p=0.048)	11.3 vs. 11	26.4 vs. 9.2 (p=0.02)
GEMCIS vs. GEM	Heinemann <i>et al</i> (48)	III	195	LA/M	7.6 vs. 6 mo (p=0.15)	5.3 vs. 3.1 mo (p=0.053)	25.3 vs. 24.7 (p=0.21)	10.2 vs. 8.2
GEMOX vs. GEM	Louvet <i>et al</i> (46)	III	313	LA/M	9.0 vs. 7.1 mo (p=0.13)	5.8 vs. 3.7 mo (p=0.04)	34.7 vs. 27.8 (p=0.22)	26.8 vs. 17.3 (p=0.04)
GEMIRI vs. GEM	Rocha-Lima <i>et al</i> (54)	III	360	LA/M	6.3 vs. 6.6 mo (p=0.789)	3.5 vs. 3.0 mo (p=0.352)	21 vs. 22	16.1 vs. 4.4 (p<.001)
GEM-EXE vs. GEM	Abou-Alfa <i>et al</i> (55)	III	349	LA/M	6.7 vs. 6.2 mo (p=0.52)	3.7 vs. 3.8 mo (p=0.22)	23 vs. 21	6.3 vs. 4.6
GEM-PEM vs. GEM	Oettle <i>et al</i> (50)	III	565	LA/M	6.2 vs. 6.3 mo (p=0.8477)	3.9 vs. 3.3 mo (p=0.11)	21.4 vs. 20.1	14.8 vs. 7.1 (p=0.004)

FU, 5-fluorouracil; GEM, gemcitabine; CAPE, capecitabine; GEMFU, GEM + FU; GEMCAPE, GEM + CAPE; GEMCIS, GEM + CDDP; GEMOX, GEM + oxaliplatin; GEMIRI, GEM + irinotecan; GEM-EXE, GEM + exatecan; GEM-PERM, GEM + pemetrexed; LA, locally advanced; M, metastatic; OS, overall survival; PFS, progression-free survival; RR, response rate.

received gemcitabine alone, with a good profile of toxicity in both arms (30). A second phase III trial randomized 329 patients in gemcitabine (1000 mg/m² on days 1, 8) plus capecitabine (1300 mg/m²/day days 1-14 every 21) arm and in the standard gemcitabine regimen arm. OS was not statistically significant different between the two arms (p=0.23). However, the patients with good baseline PS (score 90-100) who received the combination regimen had a significant improvement in survival (p=0.014) (31). A more recent phase III trial analysed the CBR and quality of life (QOL) in patients who received gemcitabine and capecitabine compared to gemcitabine alone, but did not disclose differences between the two treatment arms (32).

Gemcitabine and tegafur/UFT or S-1. Both drugs are oral fluoropyrimidines that mimic the effect of a continuous infusion of 5-FU.

UFT, a combination of 1-5-FU (tegafur) and uracil, was evaluated in addition to gemcitabine in some phase II trials with encouraging results in terms of median OS (11 months) and a median TTP (6 months) (33,34).

In 2004 Lee and colleagues obtained a median OS of 5.8 months and a median TTP of 4.2 months from the same regimen. These modest results can be explained by the

particular kind of population examined in the trial, represented only by patients with metastatic disease (35).

Ueno and colleagues reported a good anticancer activity of the combination of S-1 with gemcitabine in 18 chemotherapy-naïve patients in a phase I trial (36). A median OS of 10.1 months and a median PFS of 5.9 months were subsequently shown by a phase II study (Ueno H, *et al*, Gastrointestinal Cancers Symposium: 148, 2007). Similar data were obtained by a more recent study (Oh H, *et al*, Gastrointestinal Cancers Symposium: 212, 2008). Both the last two studies are reported in abstract form only. Nevertheless, there are no confirmatory randomized studies demonstrating the superiority of new regimens compared to gemcitabine monotherapy.

Gemcitabine and platinum compounds. Platinum derivatives are frequently used in combination schedules to treat pancreatic cancer.

Encouraging results were obtained in some phase II trials using different schedules with an overall TTP from 3.6 to 5.7 and an OS from 5.6 to 9.5 months (37-44,47). In particular, a preliminary trial assessed the combination of gemcitabine (1000 mg/m² as a 10 mg/m²/min infusion on day 1) plus oxaliplatin (100 mg/m² as a 2-h infusion on day 2 every two

Table III. Gemcitabine and cisplatin based chemotherapy regimens.

Regimen	Refs.	Type of study	No. of patients	Stage disease	Median survival (mo)	PFS (mo)	1-year survival (%)	RR (%)
GEMCIS	Heinemann <i>et al</i> (37)	II	41	LA/M	8.2	4.3	27	11
GEMCIS	Philip <i>et al</i> (39)	II	42	LA/M	7.1	5.4	19	26
GEMCIS	Cascinu <i>et al</i> (38)	II	45	LA/M	5.6	3.6	-	9
GEM vs. GEMCIS	Colucci <i>et al</i> (47)	III	107	LA/M	5 vs. 7.5 (p=0.43)	1.8 vs. 4.6 (p=0.048)	11 vs. 11.3	9.2 vs. 26.4 (p=0.02)
GEMCIS vs. GEM	Heinemann <i>et al</i> (48)	III	195	LA/M	7.6 vs. 6.0 (p=0.15)	5.3 vs. 3.1 (p=0.053)	25.3 vs. 24.7 (p=0.21)	10.2 vs. 8.2
GEMCIS	Clayton <i>et al</i> (44)	II	36	LA/M	9.5	5.7	41.7	-
GEMCIS	Ko <i>et al</i> (40)	II	51	M	7.1	3.9	29	19.1
GEMCIS	Ueno <i>et al</i> (42)	II	38	M	7.5	4.2	24	26

GEMCIS, gemcitabine + cisplatin; GEM, gemcitabine; LA, locally advanced; M, metastatic; PFS, progression-free survival; RR, response.

weeks) (GEMOX regimen) in 64 eligible previously untreated advanced pancreatic cancer patients. A median OS of 8.7 months and 11.5 months were reported in metastatic and locally advanced patients, respectively (45).

The only multicenter phase III study involving 313 advanced patients compared the GEMOX regimen to gemcitabine alone. The combination regimen offered a significant improvement of PFS (5.58 vs. 3.7 months), CBR (38.2 vs. 26.9%) and response rate (RR) (26.8 vs. 17.3%) but no advantage was seen in terms of OS (46) (Table II). Moreover, neurotoxicity and higher grade thrombocytopenia were observed in the experimental arm. Colucci and colleagues confirmed the advantage of the platinum doublet in terms of CBR and median TTP, but median OS did not reach a statistical significance (47). Heinemann and colleagues in phase III trial demonstrated an improvement in median OS for the addition of cisplatin to gemcitabine, although these data did not yield statistical evidence (48), as summarized in Table III.

Gemcitabine and pemetrexed. Pemetrexed is a multitargeted antifolate that has a synergistic activity with gemcitabine. Miller and colleagues in phase II trial tested the activity of pemetrexed as a single agent in advanced pancreatic cancer patients. They reported an OS of 6.5 months and a median time to treatment failure of 4 months (49). A phase III trial on 565 advanced pancreatic patients randomly assigned either gemcitabine plus pemetrexed or gemcitabine alone. No significant differences between the two treatment arms were observed in terms of OS and PFS (50).

Gemcitabine and topoisomerase inhibitors. Irinotecan (CPT-11) and Exatecan are the most widely used topoisomerase inhibitors in pancreatic cancer treatment. Their antitumor activity was investigated in some phase II trials, but without great emphasis (51,52). The first phase II trial to

evaluate the combination regimen with gemcitabine showed a median survival of 5.7 months and a median TTP of 2.8 months, and the phase III randomized study confirmed these data (53,54). However, other trials failed to confirm the lack of improvement in OS by the addition of the topoisomerase inhibitors to gemcitabine, and in some cases the combination led to major toxicity (55,56).

Gemcitabine and taxanes. Antitumoral action of taxanes is due to their mechanism of microtubule stabilization and consequently to the cell cycle arrest. The association of gemcitabine with paclitaxel or docetaxel in advanced pancreatic patients was studied in many phase I and II trials, but none of them showed additional clinical benefit (57-59). The major treatment-related toxicity, namely myelosuppression, precluded the development of randomized trials. Overall, these studies showed a median survival from 4.7 to 8.9 months and a RR from 12.5 to 18%, but severe neutropenia occurred in about 50% of patients in both trials (60,61).

Recently Genexol-PM, a novel micellar paclitaxel, was tested in a phase II trial in comparison to gemcitabine alone. The micellar formulation of paclitaxel had a similar efficacy to gemcitabine with a PFS and OS of 3.0 and 6.2 months respectively (Saif MW, *et al*, Gastrointestinal Cancer Symposium, abs. 269, 2008). Further trials on the genexol-PM and gemcitabine combination are planned.

4. Multidrug combination regimens

The first phase III trial to analyze the efficacy of a multi-drug combination was carried out by Reni and colleagues in 2005 comparing the activity of cisplatin, epirubicin, gemcitabine and 5-FU (PEFG) to gemcitabine alone. The PFS was about 60% in the combination arm compared to 28% in the standard arm treatment (p=0.003), the RR was about 38 vs. 8.5%,

Regimen	Refs.	Type of study	No. of patients	Stage disease	Median survival (mo)	PFS (mo)	1-year survival (%)	RR (%)	SD (%)
GEM + E vs. GEM + P	Moore <i>et al</i> (70)	III	569	M/LA	6.24 vs. 5.91 (p=0.038)	3.75 vs. 3.55 (p=0.004)	23 vs. 17 (p=0.023)	8.6 vs. 8	48.9 vs. 41.2
GEM + Cetuximab vs. GEM	Philip <i>et al</i> (76)	III	766	M/LA	6.5 vs. 6 (p=0.14)	3.5 vs. 3 (p=0.058)		12 vs. 14	
GEM + Bevacizumab vs. GEM + P	Kindler ^a	III	602	M/LA	5.7 vs. 6.0 (p=0.40)	4.8 vs. 4.3 (p=0.99)		13.1 vs. 11.3	40.7 vs. 35.7
GEM + E + Bevacizumab vs. GEM + E + P	Van Custem <i>et al</i> , (87)	III	607	M	7.1 vs. 6	4.6 vs. 3.6 (p=0.0002)		13.5 vs. 8.6	49.2 vs. 45.2
Marimastat (50 mg daily) vs. GEM	Bramhall <i>et al</i> (92)	III	414	U	4.1 vs. 5.5	1.9 vs. 3.8	20 vs. 19	2.8 vs. 25.8	
Marimastat + GEM vs. GEM	Bramhall <i>et al</i> (91)	III	239	U	5.4 vs. 5.4	3 vs. 3.1	18 vs. 17	11 vs. 16	50 vs. 56
Tipifarnib + GEM vs. GEM	Van Custem <i>et al</i> (95)	III	688	M/LA	6.3 vs. 6 (p=0.75)	3.7 vs. 3.6 (p=0.72)	27 vs. 24	6 vs. 8	53 vs. 52

GEM, gemcitabine; P, placebo; E, erlotinib; PFS, progression free survival; OR, objective response; SD, stable disease; M, metastatic; LA, locally advanced; U, unresectable. ^aKindler *et al*, ASCO Gastrointestinal Cancers Symposium, abs. 108, 2007.

respectively, and the one-year survival rate was 38 vs. 21%, respectively (p=0.11) (62). These good results led to tests on five-drug combinations such as CPT-11, gemcitabine, 5-FU, leucovorin and cisplatin (G-FLIP): OS was 8.1 months and median TTP was about 6.1 months (56). Another interesting trial assessed the efficacy of an oxaliplatin, 5-FU and folinic acid (FOLFOX-6) combination in metastatic disease. The results, OS of 7.5 months and TTP of 4 months, are encouraging and justify further study (63). A combination of 5-FU, folinic acid and CPT-11 (FOLFIRI.3) with promising activity was also evaluated in the first-line setting yielding median OS and PFS of 12.1 and 5.6 months, respectively (64).

5. Targeted therapies

Epidermal growth factor receptor (EGFR) and HER2/neu in pancreatic cancer. EGFR, also known as HER-1 (human epidermal growth factor receptor) or ErbB-1, is a 170-kDA transmembrane glycoprotein that consists of a cysteine-rich extracellular ligand binding domain, a hydrophobic transmembrane domain and a cytoplasmatic tyrosine kinase domain.

EGFR is activated by several ligands including EGF (epidermal growth factor), TGF- α (transforming growth factor α), HB-EGF (heparin-binding EGF), amphiregulin, epiregulin, betacellulin and neuregulin. Activated EGFR forms homo- or heterodimeric complexes with another member of the ErbB receptor family which in turn leads to phosphorylation of the intracellular c-terminus kinase domain and activation of downstream signalling pathways.

HER2/neu is another member of the ErbB family of transmembrane tyrosine kinase receptors which is the preferred heterodimeric partner because no EGF family ligand is able to activate it.

The main signalling pathways activated by EGFR with or without HER2/neu are Ras/MAP kinase, phosphatidylinositol 3'-kinase (PI3K)/Akt, Janus kinase (JAK)/Stat and phospholipase C/protein kinase C. Ultimately all these pathways lead to activation of genes involved in cell proliferation, migration, adhesion, differentiation and apoptosis.

Dysregulation of EGFR and HER2/neu pathways can be found in a wide array of solid neoplasms including pancreatic cancer. EGFR and some of its ligands, EGF and TGF- α , were frequently overexpressed (43, 46 and 54%, respectively) in human pancreatic carcinoma and their coexpression seems to be correlated with an increased tumor aggressiveness and poor prognosis (65).

Studies evaluating the overexpression of HER-2 in pancreatic cancer by immunohistochemical labelling have yielded widely varying results with values ranging from 0 to 82%, and only a few of these studies correlated this discrepancy to different methodologies (66,67).

Since the dysregulation of EGFR and HER2/neu pathways is involved in the proliferation, invasion and spread of cancer cells, it is a logical assumption that targeting these receptors might exert an antitumoral effect. To date, two strategies to inhibit the ErbB receptor family have been investigated clinically: inhibitors of the tyrosine kinase domain and monoclonal antibodies directed against the extracellular ligand binding domain. Table IV summarizes phase III trials involving targeted therapies in combination with gemcitabine.

Erlotinib. Erlotinib is an orally administered small tyrosine kinase inhibitor (TKI) molecule that competes with ATP (adenosine triphosphate) in binding the kinase domain and preventing downstream signal transduction.

Preliminary studies of erlotinib alone and in combination with gemcitabine showed an interesting antitumor activity, good tolerability with acne-like rash among the most common side-effects (68,69).

The National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) in cooperation with Australasian Gastro-intestinal Tumor Group (AGITG) conducted a phase III trial involving 569 chemotherapy naïve advanced pancreatic patients randomly assigned to receive either standard gemcitabine plus placebo or gemcitabine plus erlotinib (100 or 150 mg/day per os). As reported in Table IV, the median survival time and the PFS were statistically significant in the combination arm and led to the approval of erlotinib in combination with gemcitabine by the FDA as a first-line treatment for unresectable pancreatic cancer (70). Interestingly, the analysis of EGFR expression in the subgroup of patients treated with erlotinib showed no significant gain in terms of survival related to EGFR status while the presence of skin rash was associated with a significantly longer survival ($p=0.037$). Some authors assume that this result is due in part to the techniques used to determine EGFR expression and in part to involvement of the tumoral microenvironment, including endothelial cells that could play an important role in the mechanism of action of erlotinib (71).

Erlotinib has also been evaluated in combination with capecitabine in gemcitabine refractory patients in a phase II study (72). The median PFS and OS were 3.4 and 6.5 months, respectively, with 10% partial response. This combination could be a valuable second-line treatment option in those patients who received a chemotherapy regimen containing gemcitabine as a first-line chemotherapy.

Cetuximab. Cetuximab is a chimeric IgG1 monoclonal antibody that specifically binds to the extracellular domain of EGFR preventing downstream signal transduction activations. Cetuximab significantly suppresses tumoral growth and reduces microvascular density by down-regulation of tumor cell-produced VEGF (vascular endothelial growth factor) and IL-8 with inhibition of tumor-induced angiogenesis (73).

Due to the interesting results of a phase I study (74), a phase II trial was designed to determine the efficacy and tolerability of cetuximab combined with gemcitabine in pathologically confirmed EGFR-expressing pancreatic cancer patients (75). Treatment was generally well-tolerated and the development of a skin rash, in particular grades 3-4, was associated with longer survival. These encouraging results were not confirmed in the subsequent studies (76,77), as summarized in Table IV.

Gefitinib. This orally bioavailable active quinazoline tyrosine kinase inhibitor is a competitive inhibitor of ATP binding to the intracellular kinase domain of EGFR.

Fountzilias and colleagues published the results of a phase II study involving 53 inoperable or metastatic pancreatic cancer patients who received the combination of

gefitinib plus gemcitabine. Median survival time and PFS were 7.3 and 4.1 months, respectively. The one-year survival rate was 27% and partial responses and stable disease were reported in 9 and 23% of patients, respectively (78).

Gefitinib was also evaluated, as a second-line treatment, in combination with docetaxel but the combination failed to be active as a salvage treatment after failure of gemcitabine-based chemotherapy (79).

Lapatinib. Lapatinib is a small molecule, orally administered, that reversibly inhibits both EGFR and HER2/neu tyrosine kinases.

Safran and colleagues published the results of a phase I trial evaluating the safety/tolerability and antitumor activity of lapatinib in combination with either gemcitabine or with GEMOX schedule in patients with naïve advanced pancreatic and biliary cancer. Lapatinib showed a median survival of 10 months among the 16 patients with metastatic pancreatic cancer (80).

A phase II study of lapatinib in combination with gemcitabine is currently ongoing in metastatic pancreatic patients.

Trastuzumab. Trastuzumab is a HER2 recombinant humanized IgG1 monoclonal antibody with a well-established therapeutic efficacy in breast carcinoma (81). As mentioned above, HER2/neu is overexpressed in pancreatic cancer in different ways.

An *in vitro* study on pancreatic cancer cell lines showed a correlation of cell growth inhibition with the expression levels of HER2/neu. These observations were confirmed in an orthotopic mouse model (82,83).

A preliminary clinical trial evaluated the effectiveness and toxicity of trastuzumab plus gemcitabine in 34 metastatic pancreatic cancer patients with 2+/3+ HER-2/neu expression by immunohistochemistry. Only 4 patients (16%) had HER-2/neu 3+ overexpression. Confirmed partial responses were observed in 2 out of 32 patients (6%) and the median survival was 7 months.

Further studies are needed to assess the real effectiveness and role of this molecule in the treatment of pancreatic cancer (84).

6. Vascular endothelial growth factor (VEGF)

VEGF is an important mediator of tumor angiogenesis. The progressive growth and metastasis of neoplasms depend in part on angiogenesis, the extent of which is determined by the balance between pro-angiogenic and anti-angiogenic molecules released by tumor cells and normal host cells.

VEGF is able to bind to specific receptors, VEGFR-1 (vascular endothelial growth factor receptor-1) and VEGFR-2 principally, which in turn activate specific downstream proliferation and survival pathways. VEGF is overexpressed in human pancreatic cancer and is associated with disease progression (85).

Bevacizumab. Bevacizumab, a humanized monoclonal immunoglobulin G antibody, inhibits all active isoforms of VEGF. A phase II study evaluated the combination of



SPANDIDOS mab plus gemcitabine in 52 advanced pancreatic PUBLICATIONS Eleven patients (21%) had partial responses and 24 (46%) had stable disease. The six-month and one-year survival rates were 77 and 29% while the median OS and PFS were 8.8 and 5.4 months, respectively. The main grade 3 and 4 toxicities included hypertension, thrombosis, visceral perforation and bleeding (86).

These interesting results led to a phase III study that failed to confirm the previous findings (Kindler HL, *et al*, ASCO Gastrointestinal Cancers Symposium, abs. 108, 2007). Therefore, a double-blind, placebo controlled, multicenter phase III randomized trial was conducted to evaluate the efficacy and safety of the bevacizumab, erlotinib and gemcitabine combination in metastatic pancreatic cancer patients. Median OS was not statistically significant between the two treatment arms but PFS was significantly improved in the bevacizumab arm Table IV (87). Bevacizumab was also evaluated in a small multicentric phase II study in combination with gemcitabine and capecitabine in 50 advanced pancreatic patients. One patient achieved a complete response (2%), 10 partial response (20%) and 30 stable disease (60%). Median PFS and OS were 5.8 and 9.8 months, respectively (Iyer RV, *et al*, Gastrointestinal Cancers Symposium, abs. 198, 2008).

Sorafenib. Sorafenib is an oral multikinase inhibitor able to inhibit the tumor growth targeting MAPK pathway by Raf-kinase, VEGF-R2, -R3 and platelet-derived growth factor receptor (PDGFR)- β . This small oral molecule is under evaluation in some clinical trials alone or in combination with chemotherapeutic agents in many types of cancer.

The combination of sorafenib plus gemcitabine was tested in pancreatic cancer patients in two small clinical trials. A phase I study was conducted on 23 patients and 56% of them showed evidence of disease stabilization, whereas a more recent phase II trial on 17 patients showed no efficacy in advanced pancreatic cancer (88,89).

7. Other molecules

Marimastat. Matrix metalloproteinases (MMPs) are a family of zinc-dependent proteolytic enzymes responsible for the degradation of connective tissue proteins. Aberrant MMP expression contributes to the invasive growth and spread of a variety of solid malignancies (90).

The interesting results obtained in animal models were not confirmed in clinical practice. In particular, marimastat, an oral MMP, was evaluated in a randomized phase III trial in 414 locally advanced pancreatic patients yielding one-year survival rates similar to those in patients who had received gemcitabine (91). However, a subsequent phase III study failed to show any significant improvement in terms of clinical benefit of marimastat over gemcitabine alone (92).

Tipifarnib. Tipifarnib is an oral non-peptidomimetic farnesyl transferase inhibitor which demonstrated anti-proliferative effects in a wide array of tumor cell lines including those of pancreatic origin.

Farnesylation is an important post-translational event required for Ras activation. This proto-oncogene, in particular K-Ras, is frequently mutated in pancreatic cancer and is

responsible for the increased tumor proliferation, invasiveness, resistance to apoptosis and metastasis (93).

The clinical impact of Tipifarnib in pancreatic cancer has been a failure and did not improve OS either as a single agent or in combination with gemcitabine over gemcitabine alone (94,95).

8. Second-line treatments

There is still no indication for standardized second-line chemotherapy in advanced pancreatic patients, but in the last few years many trials have studied different regimes in gemcitabine pre-treated patients. The first second-line study was done by Oettle and colleagues. They proved the efficacy of the oxaliplatin and 5-FU regimen with interesting results such as an increased survival with a median value of 4.8 months compared to the 2.8 months in the BSC arm ($p=0.007$) (96).

Platinum compounds and 5-FU are also being widely studied in these patients (97). A phase II trial showed the efficacy of an oxaliplatin, leucovorin and 5-FU regimen, with a median OS of 25 weeks (98). In the wake of this study, Gebbia and colleagues proposed the FOLFOX4 regimen as a second-line therapy, obtaining a median TTP and OS of 4.0 and 6.7 months, respectively (99).

The capecitabine and oxaliplatin combination has also been tested in gemcitabine pre-treated pancreatic patients. A recent phase II showed the good activity of this combination, especially in patients with good PS; the median OS was 23 weeks and a one-year survival rates was 21% (100).

Among platinum-combination trials, the multidrug combination regimen PEFG was also studied as a second-line treatment option. Reni and colleagues showed promising results with an OS of 8.3 months and PFS of 5 months (101).

Disappointing data came from taxane combination trials: the docetaxel-gefitinib association in a phase II trial demonstrated no activity as a salvage treatment (79).

The role of topoisomerase inhibitors in gemcitabine pre-treated patients has also been discussed. CPT-11 as a single agent showed a small efficacy in terms of PFS (2.0 months) and OS (6.6 months) (102), but the combination with oxaliplatin showed a good synergistic activity in the trial of Cantore and colleagues, with a median OS value of 5.9 months and a median PFS of 4.1 months (103).

Other trials analyzed the use of pemetrexed as a second-line agent. A multicenter phase II study showed a TTP of 7 weeks and a median OS of 20 weeks, while a pemetrexed-irinotecan combination trial demonstrated moderate activity in advanced pancreatic patients after failure of gemcitabine (104).

9. Conclusions

All the studies examined in this review demonstrate and confirm that advanced pancreatic cancer is among the most complex cancers to treat. Since the approval of gemcitabine as a standard treatment for advanced pancreatic patients, no drug or combination of drugs has significantly improved the prognosis. However, gemcitabine-based regimens or more toxic schedules may be reserved for patients with good PS.

A better understanding of pancreatic cancer biology, earlier diagnosis and a better selection of patients on the basis of specific bio-pathological characteristics will help oncologists to improve the clinical management and outcome of these patients.

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