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Current Perspectives and Future Trends of Systemic Therapy in Advanced Pancreatic Carcinoma

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1. Introduction

Pancreatic carcinoma is one of the most lethal solid tumors, with particularly high mortality-to-incidence rates. Indeed, about 278,684 people were diagnosed worldwide of pancreatic cancer in 2008, of whom 266,669 dyed from the disease in the same year (Ferlay et al, 2010). The greatest impact is observed in developed countries were pancreatic cancer has become the fourth leading cause of cancer-related death (Jemal et al, 2010).

Pancreatic ductal adenocarcinoma represents more than 90% of pancreatic malignancies. The majority arise in the head, neck or uncinate process (60-70%), being less commonly encountered in the body (5-10%) or tail (10-15%) of the gland (Solcia et al, 1997). Clinical presentation is often related to the location of the primary tumor within the gland, although many patients often undergo an initial period of nonspecific symptoms such as back pain or vague gastrointestinal distress. Jaundice may be a relatively early symptom for tumors located in the head or uncinate process of the pancreas. However, left-sided pancreatic tumors may remain asymptomatic for long periods of time. Other associated disorders include acute pancreatitis or diabetes mellitus, and when they develop in patients without risk factors or in conjunction with other associated symptoms such as pain, anorexia or weight loss, the possibility of an underlying malignancy should be considered. Thromboembolic complications are also very common and are associated with a poor prognosis, with an incidence ranging from 17% to 57% (Khorana & Fine, 2004). Anorexia, weight loss or gastric outlet obstruction generally occur late in the course of the disease. Nevertheless, even early symptoms in this tumor are usually indicative of advanced disease.

Clinical features of pancreatic adenocarcinoma translate its extremely high propensity for local invasion and distant spread, underscoring the great difficulty to obtain an early diagnosis. In fact, more than 70% of patients present with unresectable, locally advanced or metastatic disease at the time of diagnosis (Stathis & Moore, 2010), and 70-80% of resected tumors will eventually relapse following surgery. Once the tumor has progressed beyond

surgical resectability, prognosis is rather poor, with median survival ranging from 6 to 9 months and 5-year overall survival rates of less than 5% (National Cancer Institute, 2010; Jemal et al, 2008).

In recent years there has been only minimal progress in the systemic treatment of metastatic pancreatic cancer. Current standard therapies have a limited impact on the natural history of this disease and improvements in systemic therapy are desperately needed in order to improve the prognosis of these patients. However, intense translational and clinical research has lead to a better and deeper understanding of the complex molecular biology of this tumor and shall help improve the development of new more effective drugs in this disease.

2. Conventional cytotoxic therapy

2.1 Monotherapy

Early randomized trials demonstrated that several 5-fluorouracil (5FU)-based combination chemotherapy regimens improved survival (hazard ratio [HR] = 0.64; 95%CI, 0.42 to 0.98) and quality of life of patients with advanced pancreatic cancer over best supportive care (BSC) alone (Sultana et al, 2007). Subsequent studies showed, however, that 5FU-based combination therapy did not result in better overall survival compared with 5FU alone (HR = 0.94; 95% CI, 0.82 to 1.08). 5FU monotherapy became, consequently, the standard of care for pancreatic cancer. Reported response rates widely ranged from 0% to 19% (Evans et al, 1997), partly due to the lack of standardized criteria to assess response in these early trials, with median survival times of 4.2 to 5.5 months (Burris et al, 1997).

During the 1990s several non-controlled trials suggested some promising activity of a new drug in pancreatic cancer, gemcitabine. The pivotal study by Burris et al was responsible for the change in practice from 5FU to gemcitabine based on a marginal survival advantage and an improvement in clinical benefit response favoring gemcitabine-treated patients. This trial enrolled 126 patients with chemotherapy-naïve advanced symptomatic pancreatic cancer who were randomly allocated to receive gemcitabine (1000 mg/m2/week x 7 followed by 1 week of rest, and then weekly x 3 every 4 weeks) or 5-FU (600 mg/m2/week) until disease progression, clinical deterioration or unacceptable toxicity (Burris et al, 1997). The primary efficacy outcome was clinical benefit response (CBR), a term introduced for the first time in this trial, which was a composite of measurements of pain (analgesic consumption and pain intensity), Karnofsky performance status and weight. No statistically significant difference was found between study arms in terms of objective response (gemcitabine 5.4% vs 5-FU 0%), but patients in the gemcitabine arm experienced improved CBR (24% vs 5%) and overall survival (5.65 months vs 4.41 months, p=0.0025), with 1-year survival rates also favoring gemcitabine-treated patients (18% vs 2%).

Further trials aimed to optimize gemcitabine administration schedule. Gemcitabine (difluorodeoxycytidine) is a nucleoside analogue capable of inhibiting ribonucleotide reductase to deplete nucleoside pools, and its phosphorylated metabolite is incorporated into DNA causing chain termination and inhibition of DNA synthesis, function and repair. Phosphorylation of gemcitabine to the monophosphate by deoxycytidine kinase is the rate-limiting step in the accumulation of the active diphosphate and triphosphate metabolites. Some early clinical studies observed the rate of gemcitabine triphosphate accumulation by mononuclear cells and leukemia cells was optimized using dose rates of 10 mg/m2/min.

Conversely, preclinical data had suggested a dose-response relationship independent of infusion duration. In light of these data, a randomized phase II trial conducted in 92 pancreatic cancer patients was designed to assess the efficacy of two dose-intense schedules of gemcitabine: a dose-intense schedule administering gemcitabine as a standard 30-minute infusion (2200 mg/2/week) versus gemcitabine administered at a fixed dose rate (FDR) of 10 mg/m2/min (1500 mg/m2/week 150-minute infusion) (Gelibter et al, 2005; Tempero et al, 2003). Patients in the FDR infusion arm experienced increased survival rates (18% vs 2% at 2 years, p=.007), consistent with the higher intracellular gemcitabine triphosphate concentrations observed in these patients, although at the expense of increased hematologic toxicity. However, a confirmatory phase III trial failed to confirm a survival advantage for the FDR regimen over the standard administration (Poplin et al, 2009).

2.2 Combination chemotherapy

Although the benefit of chemotherapy in patients with advanced pancreatic cancer is well established, the magnitude of the effect is rather small, with an absolute improvement of survival at 5 years of 3% to 6% (survival rates from 1975-77 to 1999-2005) (Oberstein & Saif, 2011). Over the past decade, multiple randomized trials have been performed to assess a number of gemcitabine-combination chemotherapy regimens in an effort to improve these modest results. These have included combinations with 5-FU (Berlin et al, 2002; Riess et al, 2005), capecitabine (Herrmann et al, 2007; Bernhard et al, 2008; Cunningham et al, 2009), cisplatin (Heinemann et al, 2006; Colucci et al, 2002, 2009), oxaliplatin (Louvet et al, 2005; Poplin et al, 2009), irinotecan (Rocha et al, 2004; Stathopoulos et al, 2006), exatecan (Abou Alfa et al, 2006) and pemetrexed (Oettle et al, 2005a). Individually, although many of these studies observed some improvement in terms of response rate and progression free survival favoring combination therapy, the great majority failed to demonstrate a survival benefit (Table 1).

The largest and most recent meta-analysis, however, confirm a modest although significant benefit in survival for gemcitabine combinations over gemcitabine alone (HR 0.91; 95%CI: 0.85 to 0.97; p=0.004) in patients with locally advanced or metastatic pancreatic cancer (Sultana et al, 2007; Heinemann et al, 2008b). The magnitude of this benefit was remarkably greater (HR 0.76; 95%CI: 0.67 to 0.87; p<0.0001) in patients with good performance status (representing 38% of all patients included in the meta-analysis). In subgroup analysis, platinum compounds (3 trials, 1077 patients; HR 0.85; 95%CI 0.74-0.96) and capecitabine (3 trials, 935 patients; HR 0.83; 95%CI 0.72-0.96) in combination with gemcitabine consistently showed improved survival over single-agent gemcitabine. Insufficient evidence was observed, nevertheless, to support combination of gemcitabine with 5FU or irinotecan.

The rationale for the combined use of gemcitabine and cisplatin is based on the preclinical evidence that gemcitabine not only increases cisplatin-induced DNA cross links, but also effectively inhibits their repair, and cisplatin, on the other hand, enhances the incorporation of gemcitabine triphosphate into DNA. In vitro studies show synergistic cytotoxicity and several non-controlled clinical studies suggested improved efficacy. Some early randomized studies observed increased response rates and progression free survival for patients treated with the cisplatin-gemcitabine combination as compared to those treated with gemcitabine alone (Colucci et al, 2002; Heinemann et al, 2006), with a non-significant trend towards a longer survival. However, more recent and larger trials have failed to confirm a significant

Reference	Treatment	Number of patients	Response Rate (%)	PFS (months)	OS (months)
Berlin *et al* (2002)	GEM vs GEM+5FU	327	5.6 vs 6.9	2.2 vs 3.4 (p=0.022)	5.4 vs 6.7 (p=0.09)
Herrmann *et al* (2007)	GEM vs GEM+ CAP	319	7.8 vs 10	3.9 vs 4.3 (p=0.103)	7.2 vs 8.4 (p=0.234)
Cunningham *et al* (2009)	GEM vs GEM+ CAP	533	12 vs 19 (p=0.034)	3.8 vs 5.3 (p=0.004)	6.2 vs 7.1 (p=0.08)
Colucci *et al* (2002)	GEM vs GEM+CIS	107	9.2 vs 26.4 (p=0.02)	1.8 vs 4.6 (p=0.048)	5 vs 7.5 (p=0.43)
Colucci et al (2010)	GEM vs GEM+CIS	400	10.1 vs 12.9 (p=0.37)	3.9 vs 3.8 (p=0.80)	8.3 vs 7.2 (p=0.38)
Heinemann *et al* (2006)	GEM vs GEM+CIS	195	8.2 vs 10.2	3.1 vs 5.3 (p=0.053)	6 vs 7.6 (p=0.15)
Louvet *et al* (2005)	GEM vs GEM+OX	313	17.3 vs 26.8 (p=0.04)	3.7 vs 5.8 (p=0.04)	7.1 vs 9 (p=0.13)
Poplin *et al* (2009)	GEM vs GEM FDR GEM+OX	832	6 vs 10 vs 9 (p=0.11)	2.6 vs 3.5 (p=0.04) vs 2.7 (p=0.1)	4.9 vs 6.2 (p=0.04) vs 5.7 (p=0.22)
Stathopoulos *et al* (2006)	GEM vs GEM+IRI	145	10 vs 15 (p=0.39)	2.8 vs 2.9 (p=0.79)	6.4 vs 6.5 (p=0.97)
Rocha Lima *et al* (2004)	GEM vs GEM+IRI	360	4.4 vs 16.1 (p<0.001)	3 vs 3.5 (p=0.352)	6.6 vs 6.3 (p=0.789)
Oettle *et al* (2005a)	GEM vs GEM+ PEM	565	7.1 vs 14.8 (p=0.004)	3.3 vs 3.9 (p=0.11)	6.3 vs 6.2 (p=0.847)
Abou Alfa *et al* (2006)	GEM vs GEM+EXA	349	4.6 vs 6.3	3.8 vs 3.7 (p=0.22)	6.2 vs 6.7 (p=0.52)

5FU, 5-fluoruracil; GEM, gemcitabine; CAPE, capecitabine; CIS, cisplatin; OX, oxaliplatin; IRI, irinotecan; EXE, exatecan; PEM, pemetrexed; RR, response rate; PFS, progression free survival; OS, overall survival.

Table 1. Selected phase III trials of gemcitabine-based chemotherapy in advanced pancreatic cancer

impact on overall survival, whereas combination therapy was associated with greater hematological toxicity (Colucci et al, 2010). Similar findings have been observed with the combination of gemcitabine with oxaliplatin (GEMOX). GEMOX was superior to gemcitabine in terms of response rate (26.8% v 17.3%; p=0.04), progression-free survival (5.8 v 3.7 months; p=0.04), and clinical benefit (38.2% v 26.9%; p=0.03), with a trend for an improved survival (9.0 v 7.1 months, p=0.13) (Louvet et al, 2005). Severe toxicities were

however more commonly induced by the combination, particularly thrombocytopenia, emesis and neurotoxicity. More recently published trials, again, did not confirm these benefits for the GEMOX regimen (Poplin et al, 2009).

Combination of gemcitabine plus capecitabine is the other cytotoxic chemotherapy doublet that has shown some advantage over gemcitabine alone. Two recent phase III studies consistently demonstrated a gain in terms of progression free survival (PFS) for the combination, although the benefit in overall survival (OS) only achieved statistical significance in the meta-analysis of these trials (Cunningham et al, 2009; Herrmann et al, 2007). Cunningham et al randomized 533 patients to receive gemcitabine (1000 mg/m2 in 30-min infusion weekly x 3 every 4 weeks) plus capecitabine (830 mg/m2/12 hours day 1-21 every 28 days) versus gemcitabine alone. Combination therapy obtained higher response rates (19.1% vs 12.4%, p=0.034) and PFS (5.3 vs 3.8 months; HR 0.78, 95% CI 0.66-0.93, p=0.004) and a trend toward better OS of borderline significance (7.1 vs 6.2 months; HR 0.86, 95% CI 0.72-1.02, p=0.08). Herrmann and colleagues randomized 319 patients to receive either gemcitabine (1000 mg/m2 days 1 and 8 every 21 days) plus capecitabine (650 mg/m2/12 hours days 1-14 every 21 days) or gemcitabine alone (1000 mg/m2 weekly for 7 weeks and one week off, and then weekly x 3 every 4 weeks). No significant differences were observed among study arms in terms of response rate, clinical benefit or quality of life (Bernhard et al, 2008), and the primary endpoint of the study, OS, was not reached (8.4 vs 7.2 months, p=0.234). However, post hoc analysis did show a significant survival advantage for the gemcitabine-capecitabine combination in patients with good performance status (10.1 vs 7.4 months, p=0.004). In both studies toxicity in the combination arm was tolerable, with a low incidence of grade 3-4 adverse events, being neutropenia and diarrhea the most commonly encountered toxicities. In light of these results, treatment with gemcitabine plus capecitabine may be considered in fit patients with advanced pancreatic cancer.

Other multidrug combinations have also been investigated over the past years in several phase II-III trials, including PEFG (cisplatin, epirubicin, gemcitabine and 5-FU) (Reni et al, 2005), G-FLIP (irinotecan, gemcitabine, 5-FU, leucovorin and cisplatin) (Goel et al, 2007), and active schedules in other gastrointestinal cancers such as FOLFOX-6 (oxaliplatin, 5-FU and folinic acid) (Ghosn et al, 2007) or FOLFIRI.3 (irinotecan, 5-FU and folinic acid) (Taïeb et al, 2007). Increased tumor responses and progression free survival have been reported for some of these regimens (Reni et al, 2005), although at the expense of a worse toxicity profile with no impact on survival. However, the combination of Gemcitabine and *nab*-paclitaxel, an albumin-bound formulation of paclitaxel particles (Celgene, Summit, NJ), deserves special mention (Von Hoff et al, 2011). *nab*-Paclitaxel has shown antitumor activity in various advanced cancer types that overexpress the albumin-binding protein SPARC (secreted protein acidic and rich in cysteine), including breast, lung, and melanoma. Results of the phase I/II trial of this combination, with an overall response rate of 48%, a median survival of 12.2 months, and a 1-year survival rate of 48% at the MTD are among the highest ever reported for a phase II study in patients with advanced pancreatic cancer. Interestingly, SPARC expression in the stroma, but not in the tumor, was correlated with improved survival (median survival of 17.8 *v* 8.1 months for high- vs low- SPARC tumors, respectively; *P*= .0431), suggesting SPARC could be a potential new predictive biomarker of nab-paclitaxel activity. This promising results have prompted the conduction of a large international phase III study that is close to complete accrual. Also recently reported, results

of the PRODIGE 4/ACCORD 11 trial comparing gemcitabine alone (1000 mg/m2 weekly x 7 every 8 weeks and then weekly x 3 every 4 weeks) to FOLFIRINOX (oxaliplatin 85 mg/m2, irinotecan 180 mg/m2, 5-FU 400 mg/m2 given as a bolus followed by 2400 mg/m2 given as a 46-hour continuous infusion; and leucovorin 400 mg/m2; every 2 weeks) demonstrated remarkable and significant improvements in response, progression free and overall survival rates favoring patients treated with FOLFIRINOX (31% vs. 9%, 6.4 months *vs*. 3.3 months, and 11.1 months *vs*. 6.8 months, respectively) (Conroy, 2011). These results are somewhat surprising, given the known modest activity of each of the individual drugs included in the regimen, and shall be confirmed. In addition, the higher toxicity profile of this combination limits its widespread use as standard of care in patients with metastatic disease, often frail. However, it may be an excellent option for carefully selected patients, particularly those with locally advanced borderline resectable disease. Anyhow, this is the first phase III randomized trial that has demonstrated a benefit in overall survival of unquestionable clinical relevance for patients with advanced pancreatic cancer, and it may change the classical paradigm of gemcitabine as the keystone in the management of advanced pancreatic cancer.

2.3 Gemcitabine-resistant disease

Once the disease progresses to gemcinatine-based therapy there is no accepted standard of care and most patients will not be suitable candidates for further therapy due to clinical deterioration. Second-line chemotherapy may be considered, however, in patients who maintain good performance status, although efficacy in this setting is questionable. Overall, it is estimated that approximately 30% of patients are in good condition (including good performance status and adequate organ function) for consideration of second-line treatment (Gounaris et al, 2010). A number of trials have been performed assessing the efficacy of different antineoplastic agents in this context. Most of the published evidence, however, consists of small phase II studies testing a variety of drugs in a heterogeneous population.

Oxaliplatin-fluoropyrimidine doublets are probably the chemotherapy regimens most widely evaluated in gemcitabine-resistant disease. Several small phase II studies showed some promising activity with different combinations of oxaliplatin and 5FU or capecitabine (FOLFOX, OFF, XELOX,..), with median survival (6-7 months) that did not substantially differed from that observed in chemotherapy-naïve patients (Tsavaris et al, 2005; Xiong et al, 2008). These results prompted the development of a phase III study (Charité Onkologie; CONKO 003) that aimed to evaluate the efficacy of the OFF regimen (oxaliplatin, fluorouracil and folinic acid) compared with best supportive care in gemcitabine-pretreated patients. Unfortunately, the control arm was closed after 46 of the planned 165 patients were enrolled due to clinician reluctance to enroll in a no-treatment arm (Oettle et al, 2005b). The results of this initial cohort, however, showed a substantial improvement in overall survival for treated patients (22 vs 10 weeks, p=0.0077). The trial design was then modified to include an alternative comparator arm consisting of 5FU plus folinic acid (FF regimen) and 165 patients were subsequently enrolled. Toxicity was acceptable with few grade 3-4 adverse events. Median progression-free survival and overall survival were significantly better in the OFF arm (13 vs 9 weeks, p=0.012, and 26 vs 13 weeks, p=0.014, respectively) (Pelzer et al, 2008).

Combining gemcitabine and oxaliplatin (GEMOX) has been another commonly evaluated therapeutic schedule. Two small non-controlled trials investigated the efficacy of oxaliplatin plus fixed-dose rate gemcitabine in patients who had progressed on single agent gemcitabine. Although reported response rates were relevant (21-24% of partial responses), toxicity was not negligible, with up to half of the patients developing at least one grade 3 adverse event (Demols et al, 2006, as cited in Gounaris et al, 2010; Fortune el al, 2009, as cited in Gounaris et al, 2010). These results, together with the findings of the phase III E6201 conducted in chemotherapy-naïve patients failing to demonstrate a survival advantage for the combination, do not warrant further evaluation of this regimen in the second-line setting (Poplin et al, 2009).

Irinotecan has been tested both as single agent and in combination with oxaliplatin or fluoropyrimidines showing some activity and an acceptable toxicity profile (Yi et al, 2009; Cantore et al, 2004). A direct comparison between oxaliplatin- and irinotecan-based regimens was made by Hwang and colleagues in a small randomized phase II trial (Hwang et al, 2009). Sixty patients were enrolled and randomly allocated to receive FOLFOX (oxaliplatin, folinic acid and infusional 5FU) or FOLFIRI.3 (the same folinic acid and 5FU schedule combined with irinotecan) after gemcitabine failure. No significant differences were observed among study arms neither in PFS (1.4 vs 1.9 months, $p>0.05$) nor in OS (4 months both regimens). In light of these results, both regimens may be reasonable options for second-line therapy in appropriately selected patients with advanced pancreatic cancer. Other irinotecan-based regimens including combinations with raltitrexed (Ulrich-Pur, 2003, as cited in Gounaris, 2010), docetaxel (Ko et al, 2008), docetaxel and mitomycin C (Reni et al, 2004) or ifosfamide (Cereda et al, 2011) have not achieved positive results in small phase II trials.

Rubitecan, an orally bioavailable camptothecin derivative, was the subject of the largest study conducted in gemcitabine-resistant pancreatic cancer, despite results of an initial single arm study were not particularly encouraging (median TTP and OS of 1.9 and 3 months, respectively). Subsequently, a large phase III study was launched the results of which have only been reported in abstract form (Jacobs et al, 2004). Four-hundred and nine patients were randomized to receive treatment with rubitecan or physician's best choice (chemotherapy 89%, supportive care only 11%). There were more responses in the rubitecan arm (11% vs. 1%) and the difference in median PFS, although clinically modest, reached statistical significance (1.9 vs. 1.6 months). There was no significant difference however in OS (3.5 vs 3.1 months, respectively).

Other tested drugs in this setting, such as taxanes or pemetrexed, have not shown particularly promising results in small studies (Gounaris et al, 2010; Boeck et al, 2007b; Mazzer et al, 2009). Multidrug combinations such as PEFG (cisplatin, epirubicin, 5-FU and gemcitabine) (Reni et al, 2008, as cited in Gounaris et al, 2010) or G-FLIP (gemcitabine, irinotecan, folinic acid, 5-FU and cisplatin) (Kozuch et al, 2001, as cited in Gounaris, 2010) appear to show improved efficacy with impressive median survival of 8.3 and 10.3 months, respectively. Selection bias may at least partially explain these outstanding results as reported toxicity was rather high, which in any case would limit their use in the general population.

3. Molecularly targeted therapies

Pancreatic adenocarcinoma is a malignant disease that results from the successive accumulation of gene mutations (Vogelstein & Kinzsler, 2004) evolving from premalignant

lesions in the ductal epithelium to invasive cancer. These include activating mutations of KRAS2 oncogene (90% of pancreatic tumors), and inactivation of the tumor-suppresor genes CDKN2A (95%), TP53 (50-75%) or DPC4 (50%). More recent comprehensive genetic analysis have shown that molecular features in pancreatic cancer may be extremely complex and heterogeneous (Jones et al, 2008), although these genetic abnormalities may be classified in 12 core cancer signaling pathways involving not only pancreatic cancer cells but also other fundamental components of neoplasia such as cancer stem cells and tumor stroma (Hidalgo, 2010). As molecular pathways governing pancreatic cancer development are unraveled, novel targets emerge that may provide some promise to improve the dismal results obtained with conventional cytotoxic therapy.

3.1 EGFR-RAS-MEK-ERK pathway

EGFR (epidermal growth factor receptor), also known as HER-1 or ErbB-1, is activated by several ligands that include EGF (epidermal growth factor), TGF-α (transforming growth factor alpha), HB-EGF (heparin-binding EGF), amphiregulin, epiregulin, betacellulin and neuregulin. Activated EGFR forms homo- or heterodimeric complexes with other members of the ErbB family, triggering downstream signaling pathways such as Ras/MAP kinase, phosphatidylinositol 3′-kinase (PI3K)/Akt, Janus kinase (JAK)/Stat and phospholipase C/protein kinase C, that ultimately activate genes involved in cell proliferation, migration, adhesion, differentiation and apoptosis (Di Marco et al, 2010). Overexpression of EGFR and its ligands is very common in pancreatic cancer, and it is linked to increased tumor aggressiveness and poor prognosis. Preclinical studies have shown that blocking EGFR signaling inhibits growth and metastasis of pancreatic tumors in xenograft models and synergistic activity has been documented when combined with gemcitabine (Tempero et al, 2011).

Two strategies to antagonize EGFR signaling have been evaluated in the clinic to date: inhibition of the tyrosine kinase intracellular domain by small molecules and EGFR inhibition by monoclonal antibodies directed against the extracellular ligand binding domain. Erlotinib is an oral tyrosine kinase inhibitor [TKI] against EGFR, and the only targeted drug that has demonstrated some efficacy in pancreatic cancer thus far. The National Cancer Institute of Canada PA.3 trial was a phase III randomized study evaluating standard gemcitabine plus erlotinib (100 or 150 mg/day) versus gemcitabine plus placebo in 569 patients with chemo-naïve advanced pancreatic cancer (Table 2). Both PFS (PFS 3.75 vs 3.55 months, HR 0.77, p=0.004) and OS (6.24 vs 5.91 months, HR 0.82, p=0.038) were significantly improved in the experimental arm (Moore et al, 2007). Most common toxicity was, as expected, diarrhea and skin rash, which were of grade 1-2 in the majority of cases without negatively impacting patient´s quality of life. Interestingly, patients that developed grade 2 or higher skin rash had significantly longer survival compared to those who developed mild or no rash (10.5 vs 5.8 vs 5.3 months, respectively, HR 0.74, p=0.037). Levels of EGFR expression, however, were not correlated with survival. This was the pivotal study that granted erlotinib marketing authorization by regulatory authorities, although the small magnitude of benefit has precluded widespread acceptance by oncologists in Europe of the gemcitabine-erlotinib combination as the new standard of care for first line therapy of advanced pancreatic cancer.

One potential explanation for this modest effect of EGFR inhibition in pancreatic cancer is the fact that KRAS mutations occur in 70-90% of these tumors (Tempero et al, 2011). KRAS

Reference	Treatment	Number of patients	OS (months)	PFS (months)	RR (%)
Moore et al (2007)	GEM + PLA vs GEM+ERLOT	569	5.91 vs 6.24 (p=0.038)	3.55 vs 3,.75 (p=0.004)	8 vs 8.6
Philip et al (2007)	GEM vs GEM+CETUX	766	6 vs 6.5 (p=0.14)	3 vs 3.5 (p=0.058)	14 vs 12
Van Cutsem et al (2009)	GEM+ERLOT+PLA vs GEM+ERLOT+BEV	607	6 vs 7.1	3.6 vs 4.6 (p=0.0002)	8.6 vs 13.5
Kindler et al (2010)	GEM+PLA vs GEM+BEV	602	5.9 vs 5.8 (p=0.95)	2.9 vs 3.8 (p=0.07)	10 vs 13
Moore et al (2003)	GEM vs BAY 12-9566	277	6.59 vs 3.74 (p<0.01)	3.5 vs 1.68 (p<0.01)	-
Bramhall et al (2001)	GEM vs MARIMASTAT	414	5.5 vs 4.1	3.8 vs 1.9	25.8 vs 2.8
Bramhall et al (2002)	GEM vs GEM+MARIMASTAT	239	5.4 vs 5.4	3.1 vs 3	16 vs 11
Van Cutsem et al (2004)	GEM vs GEM+TIPIFARNIB	688	6 vs 6.3 (p=0.75)	3.6 vs 3.7 (p=0.72)	8 vs 6

GEM, gemcitabine; PLA, placebo; ERLOT, erlotinib; BEV, bevacizumab; RR, response rate; PFS, progression free survival; OS, overall survival

Table 2. Selected phase III trials of targeted agents in advanced pancreatic cancer

functions downstream of the EGFR signaling pathway, and mutations in the KRAS protein lead to constitutive activation independent of extracellular stimuli. This is a well established mechanism of resistance to EGFR blockade in colorectal cancer, and, indeed, EGFR-targeted therapy is only to be used in KRAS wild-type tumors. The potential predictive value of KRAS mutation status and EGFR gene copy number in pancreatic cancer was evaluated in 26% of the patients included in the PA.3 trial who had tumor samples available for analysis. KRAS mutations were detected in 79% of tested samples. EGFR copy number was not correlated with treatment effect. However, the HR of death between gemcitabine/erlotinib and gemcitabine/placebo was 1.07 for patients with KRAS-mutated tumors versus 0.66 for those with KRAS wild-type tumors. Although this difference did not reach statistical significance probably due to small numbers, this plausible trend shall be further evaluated to try to improve patient selection and therapeutic benefit.

Erlotinib has also been tested as second-line treatment of patients with advanced disease. Kulke et al evaluated the combination of erlotinib and capecitabine in 30 patients with gemcitabine-refractory pancreatic cancer. Objective radiologic responses were observed in 10% of patients and the median survival was 6.5 months. In addition, 17% of treated patients experienced decreases in tumor marker (CA 19-9) levels of more than 50% from baseline. However, common toxicities, particularly diarrhea and skin rash, were significant and required treatment dose reductions in 66% of patients (Kulke et al, 2007). More recently, this treatment regimen has been tested against erlotinib-gemcitabine in a phase III AIO trial. This trial included 279 chemotherapy naïve patients that were randomly allocated to receive

capecitabine-erlotinib versus gemcitabine-erlotinib as the control arm. Crossover to gemcitabine or capecitabine alone was allowed at the time of progression. Neither time to treatment failure of second-line therapy (TTF2), which was the primary endpoint of the trial, nor OS were significantly different among study arms (TTF2 4.4 vs 4.2 months, HR 0.98, p=0.43; OS 6.9 vs 6.6 months, HR 0.96, p=0.78). Of note, overall survival was significantly correlated with KRAS mutation status (8.0 months vs 6.6 months for KRAS wild-type versus mutated tumors, respectively; HR 1.62; p=0.011). However, the study design, which included erlotinib in both treatment arms, does not allow to elucidate whether KRAS mutation status is predictive of efficacy of EGFR-targeted therapy or just a prognostic factor independent of therapy (Boeck et al, 2010). Anyhow, this regimen may represent an acceptable treatment option in patients who experience treatment failure with standard gemcitabine first-line therapy or for whom gemcitabine may not be an appropriate treatment option.

The other strategy to antagonize EGFR signaling consists of monoclonal antibodies directed against the extracellular domain of the receptor, such as cetuximab or panitumumab. They are currently approved for treatment of other advanced malignancies such as colorectal or head and neck cancer. Preclinical and early clinical trials suggested some efficay too in pancreatic cancer. Disappointingly, a large phase III trial comparing the combination of cetuximab plus gemcitabine vs gemcitabine alone (Table 2), which enrolled 366 patients, did not demonstrate a benefit in survival for the combination regimen (Philip et al, 2007). Other approaches explored include dual EGFR inhibition (TKI inhibitors plus monoclonal antibodies). Preliminary results of a phase II randomized study suggest a small benefit in terms of PFS (3.3 months vs 2.0 months) for the addition of panitumumab to gemcitabine-erlotinib, although statistical significance was not reported and final data including overall survival are awaited for definitive conclusions (Kim et al, 2010).

Lapatinib, an oral TKI which reversibly inhibits both EGFR/HER1 and HER2/neu, has also been evaluated. Preclinical assays suggested activity alone and in combination with other drugs such as capecitabine. Moreover, a phase I trial combining lapatinib with either gemcitabine or GEMOX showed encouraging results with median survival of 10 months (Safran et al, 2008, as cited in Di Marco et al, 2010). More recently, preliminary results of a single arm phase II trial evaluating the combination of capecitabine and lapatinib as first-line treatment in advanced pancreatic cancer have been presented. Survival of 6 months was not reached in 7 of the 9 enrolled patients, and none of them obtained objective responses (McDermott et al, 2011). This data led to the premature termination of the study.

HER2 may be also targeted by monoclonal antibodies such as trastuzumab. HER2 is overexpressed in some pancreatic cancers, with results widely varying from 0 to 82% in different studies. One early trial evaluated gemcitabine plus trastuzumab in 34 metastatic pancreatic cancer patients with 2+/3+ Her2-positive tumors determined by immunohistochemistry. Only 4 patients (12%) presented Her2 neu 3+ expression. Partial responses were observed in 6% of patients (2/32) (Safran et al, 2004). Further studies would be needed to appropriately assess the role of this agent in pancreatic cancer.

Other therapeutic strategies have aimed to target some of the downstream effectors of EGFR. The high incidence of KRAS mutations in pancreatic cancer provided a strong rationale for the evaluation of KRAS inhibition. Tipifarnib was the first agent of this class to

be tested. It is a farnesyl transferase inhibitor which demonstrated antiproliferative activity in a wide range of tumors in preclinical models. Farnesylation is an impotant post-traslational event required for Ras activation. A large phase III clinical trial, however, failed to demonstrate an improvement in survival of adding tipifarnib to gemcitabine over gemcitabine alone in patients with advanced pancreatic cancer (Table 2) (Van Cutsem et al, 2004). Some authors have postulated as a potential explanation for these negative results the fact that KRAS mutation could be an early event in the development of pancreatic cancer, becoming cancer cells less dependent on this pathway as the disease progresses. In addition, other mechanisms involved in the regulation of Ras activation (i.e. prenylation by other enzymes) may limit the therapeutic success of farnesyl transferase inhibition (Lobell R et al, 2001, as cited in Stathis & Moore, 2010).

Other agents targeting downstream effectors of the EGFR pathway currently under evaluation include MEK inhibitors. Phase I trials have established the recommended dose for further clinical development and have documented rash, diarrhea and central serous retinopathy as dose limiting toxicities, all of them reversible (Messersmith et al, 2011). Several phase I and II trial combining MEK inhibitors with standard chemotherapy and other targeted agents are ongoing, the results of which are awaited with great interest.

3.2 Antiangiogenic agents

Angiogenesis is a widely validated target for cancer therapy. Overexpression of vascular endothelial growth factor (VEGF) and its receptors (VEGFRs) has been described in pancreatic cancer and correlated with disease progression and poor prognosis. Bevacizumab is a recombinant humanized anti-VEGF monoclonal antibody and the most widely tested antiangiogenic agent. Promising data of several bevacizumab combination regimens in phase II clinical trials, with response rates of up to 24% and median survival of up to 11 months (Kindler et al, 2005; Walkins et al, 2010; Iyer et al, 2008, as cited in Di Marco et al, 2010), encouraged the development of two large phase III trials that unfortunately failed to yield positive results. The first one enrolled 602 patients that were randomized to receive gemcitabine plus bevacizumab or gemcitaine plus placebo. No significant differences were observed among study arms neither in PFS (PFS 3.8 vs 2.9 months) nor in OS (5.8 vs 5.9 months) (Kindler et al, 2010). The second one evaluated the addition of bevacizumab to the gemcitabine-erlotinib doublet (Table 2). Although PFS was better for the experimental arm (4.6 vs 3.6 months, HR 0.73, p=0.0002), the primary objective of the study was not met as the addition of bevacizumab did not improve overall survival (7.1 vs 6.0 months, HR 0.89, p=0.2) (Van Cutsem et al, 2009). A correlation between development of skin rash and improvement in survival was observed in this trial.

Other broadly tested agents that interfere with angiogenesis include small molecules targeting multiple kinases such as axitinib or sorafenib. Axitinib, an oral inhibitor of VEGFR-1, VEGFR-2 and VEGFR-3, was initially evaluated in a phase II randomized trial in combination with gemcitabine versus gemcitabine alone. This trial enrolled 103 patients and showed a small improvement in survival favoring the combination arm (6.9 vs 5.6 months), although this difference did not reach statistical significance (Spano et al, 2008). Nevertheless, a phase III trial was undertaken but was prematurely discontinued due to

the lack of benefit observed in an interim analysis for the addition of axitinib to the standard gemcitabine therapy. Sorafenib has also been evaluated in combination with both gemcitabine and gemcitabine-erlotinib in different non-controlled trials with disappointing results (Wallace et al, 2007; Cohen et al, 2011). The lack of success of antiangiogenic strategies in pancreatic cancer could be potentially related to the fact that most tumors display intense fibrosis and are of hypovascular nature (Stathis & Moore, 2010).

3.3 Matrix metalloproteinases (MMP) inhibitors

MMPs are a family of zinc-dependent proteolytic enzymes implicated in the degradation of extracellular matrix proteins both in physiological and pathological conditions. Aberrant MMP expression contributes to neovascularization, dissemination and metastasis of a variety of solid malignancies (Stathis & Moore, 2010). Several compounds developed to inhibit MMPs have been completely unsuccessful in clinical trials over the last decade. Marimastat was the first agent to be tested (Table 2). Two large phase III trials enrolling over 900 patients showed marimastat, either alone or in combination with gemcitabine, was not able to improve survival or disease control of patients with advanced pancreatic cancer (Bramhall et al, 2001, 2002). Similar negative results were obtained with other agents of this class. Standard gemcitabine monotherapy was compared to BAY 12-9566, in a design that allowed for crossover after disease progression. Interim analyses demonstrated a deleterious effect on survival of the MMP inhibitor as compared to the control arm (OS 3.74 vs 6.59 months, $p<0.01$), and led to early trial termination (Moore et al, 2003). In light of this data, this approach has been definitively abandoned.

3.4 Other pathways

Phosphatidylinositol-3-kinase (PI3K)/Akt/mTOR

The PI3K/Akt/mTOR pathway is determinant for processes related to cell proliferation and inhibition of apoptosis, and constitutive activation of this pathway has been documented in pancreatic cancer (Royal et al, 2008). NVP-BEZ235 is a novel dual PI3K/mTOR inhibitor that has demonstrated activity in both human pancreatic cancer cell lines and mice models, and some synergy has been observed when combined with gemcitabine and antiangiogenic EMAP II (endothelial monocyte activating polypeptide II) (Awasthi et al, 2011). Further research will define the role of these new drugs in pancreatic cancer.

Src kinase

Src tyrosine kinase is a non-receptor protein implicated in tumor progression. It is overexpressed in more than two thirds of pancreatic adenocarcinomas. Src inhibitors (dasatinib, saracatinib) have been developed demonstrating antitumor activity in cancer cell lines and mice models (Royal et al, 2008). A recent phase II trial tested saracatinib (AZD0530) in 19 gemcitabine-refractory patients. No responses were seen and the minimum of 18% 6-month survival required for continuation of the trial was not achieved. A pharmacodiagnostic pre-selection strategy is planned to be implemented to better define patients most likely to respond (Nallapareddy et al, 2010).

IGF-1R

IGF-1R mediated signaling plays an important role in cell growth regulation and survival. Several monoclonal antibodies targeting IGF-IR have undergone clinical investigation (AMG479, MK0646, R1507). Based on promising preclinical and early clinical data, a phase III trial has been initiated to evaluate the combination of AMG479 plus gemcitabine in first-line metastatic pancreatic cancer (Hidalgo, 2010).

TNF-α

TNF-α shows potent anticancer activity, but high systemic toxicity limits its use. AdEgr.TNF.11D (TNFerade) is a gene delivery strategy to increase local peritumoral TNF concentrations through intratumoral injections of an adenoviral vector expressing hTNF, in an attempt to improve local activity while minimizing systemic effects. Effectiveness in combination with gemcitabine has been demonstrated in human pancreatic xenografts (Murugesan et al, 2009). A phase III trial is currently evaluating the addition of TNFerade to 5-FU plus radiotherapy in unresectable pancreatic cancer (Stathis & Moore, 2010).

Multikinase inhibitor

Masitinib is a multikinase inhibitor that has greater activity and selectivity against KIT than imatinib. Masitinib also potently inhibits PDGFR (platelet-derived growth factor receptor) and the intracellular kinase Lyn, and to a lesser extent, FGFR3 (fibroblast growth factor receptor 3). Synergistic activity with gemcitabine was demonstrated in preclinical assays. A phase II trial combining gemcitabine and masitinib in 22 patients reported median PFS of 6.4 months and OS of 7.1 months, with a 23% 18-months survival rate. Toxicity was acceptable, being cytopenia, diarrhea and rash the most common severe events (Hammel et al, 2009). A subsequent phase III trial is ongoing comparing gemcitabine with or without masitinib.

Death receptors

AMG655 is a monoclonal antibody against human death receptor 5 (DR5) that activates caspases and, as a result, induces apoptosis in tumor cells. It showed preclinical activity and synergy with gemcitabine. Early clinical data from a phase I trial that included 13 patients reported promising results for the combination of AMG655 with gemcitabine, with a response rate of 31%, median PFS of 5.3 months and a 6-month survival rate of 76.8%. Toxicity was however not negligible, with severe adverse events observed in 69% of patients (Kindler et al, 2009). A phase II is ongoing to assess efficacy and further characterize the safety profile of this combination.

Other pathways

Other pathways highly implicated in pancreatic tumorigenesis are at earlier stages of investigation. Hedgehog, Notch and Wnt signaling are important developmental pathways related to pancreatic cancer stem cells, and new agents are being developed to target these pathways (GDC-0449, IPI-926,..). Other agents in development include monoclonal antibodies against cell-membrane proteins such as mesothelin (MORAb-009). Specific mechanisms of cell killing are still not well defined but preclinical research suggest a role in pancreatic cancer (Hidalgo, 2010).

4. Conclusions

Pancreatic cancer continues to be a major challenge for oncologists as it is a highly chemoresistant malignancy carrying an extremely poor prognosis. Despite the intense research carried out over the last decades no major improvements have been achieved in patient's outcomes. Most patients present with locally advanced or metastatic disease and will therefore require systemic therapy. Conventional chemotherapy modestly improves survival and quality of life of patients with advanced disease. Gemcitabine has been the reference treatment for over a decade and little progress has been made since its introduction in clinical practice in 1997. Gemcitabine-combination therapy with capecitabine, platinum agents or erlotinib may be considered in patients with good performance status, although the small magnitude of benefit they confer shall be balanced against the increased toxicity they induce, particularly considering that prognosis is in any case rather poor and symptomatic relief shall be a major objective of disease management. FOLFIRINOX may be a preferred option for carefully selected fit patients, particularly those with locally advanced borderline resectable disease.

Nevertheless, there is much room for improvement, and more efforts in basic, translational and clinical research will be necessary in the following years for progress to be made. Indeed, a better understanding of the biology of pancreatic cancer shall enable the discovery of new targets of potential diagnostic or therapeutic interest. Meanwhile, as the molecular pathways governing pancreatic cancer are unraveled, efforts shall be made to improve selection of patients most likely to benefit from specific therapies (SPARC, kras,..). Small randomized phase II trials of both non-selected and enriched patient populations will help to adequately identify potentially active new agents. Phase III trials should only be initiated in appropriate patients based on strong clinical and biological grounds. In this context, the need for further collaborative research is highly warranted.

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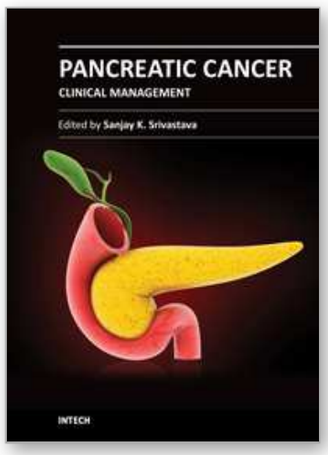

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This book covers pancreatic cancer risk factors, treatment and clinical procedures. It provides an outline of pancreatic cancer genetic risk factors, biomarkers and systems biology for the better understanding of disease. As pancreatic cancer suffers from lack of early diagnosis or prognosis markers, this book encompasses stem cell and genetic makers to identify the disease in early stages. The book uncovers the rationale and effectiveness of monotherapy and combination therapy in combating the devastating disease. As immunotherapy is emerging as an attractive approach to cease pancreatic cancer progression, the present book covers various aspects of immunotherapy including innate, adaptive, active, passive and bacterial approaches. Management of anesthesia during surgery and pain after surgery has been discussed. Book also takes the reader through the role of endoscopy and fine needle guided biopsies in diagnosing and observing the disease progression.

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