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Recent developments in the pharmacological treatment of advanced pancreatic cancer

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Metastatic pancreatic cancer is one of the leading causes of cancer-related death in North America and Europe. The high mortality rate associated with pancreatic cancer is related to the fact that the vast majority of patients develop incurable, metastatic disease. Such patients have, in the past, had few treatment options. In recent years, however, the systemic administration of gemcitabine has been accepted as a standard first-line treatment for patients with advanced pancreatic cancer. While treatment with gemcitabine has been shown to result in both clinical benefit and in prolongation of survival, objective tumour responses following therapy with gemcitabine are relatively uncommon and median survival times remain short. Current efforts have, therefore, focused on evaluating chemotherapy regimens in which gemcitabine is combined with a second cytotoxic agent. Several such combinations appear to be associated with higher objective response rates than single-agent gemcitabine and have been well-tolerated in early clinical trials. Ongoing, prospectively randomised clinical trials will help better define the efficacy of these new combinations and will determine if they result in a significant benefit when compared to gemcitabine monotherapy. A number of novel chemotherapeutic and biological agents also appear promising and are likely to play a future role in the treatment of patients with advanced pancreatic cancer.

Keywords: chemotherapy, gemcitabine, pancreatic cancer, systemic therapy

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1. Introduction

An estimated 28,000 new cases of pancreatic cancer occur in the US each year. Although pancreatic cancer is only the ninth most common cancer in the US, it is the fourth leading cause of cancer-related death. The high mortality rate associated with pancreatic cancer is attributable to the fact that the majority of patients with pancreatic cancer present with advanced stage disease. Less than 20% of patients with pancreatic cancer are diagnosed at a time when the tumour is still confined to the pancreas and can be surgically removed. Uncertainty about the efficacy of systemic therapy and a high incidence of patient comorbidities have further led to the perception of pancreatic cancer as a largely untreatable disease.

The systemic administration of 5-fluorouracil (5-FU) has historically been one of the only treatments available to patients with metastatic pancreatic cancer. Unfortunately, the response rates associated with 5-FU are low and attempts to combine 5-FU with other chemotherapeutic agents have shown little additional benefit. In the mid-1990s, gemcitabine became available for the treatment of pancreatic cancer. Based on evidence of improvements in median survival and clinical benefit,

gemcitabine has now become the standard first-line therapy for patients with metastatic pancreatic cancer.

While single-agent gemcitabine is now a broadly accepted treatment regimen for pancreatic cancer, it is still associated with an objective tumour response rate of < 10%. Furthermore, the median survival time for patients with metastatic pancreatic cancer is < 6 months [1]. In an effort to improve upon these statistics, several investigators are exploring the use of gemcitabine-based combination chemotherapy regimens. Ongoing clinical trials should help determine which of these combinations may be the most promising and which may offer patients improved overall survival and quality of life when compared to gemcitabine monotherapy. Several promising novel agents are also being investigated and may play a role in the future treatment of patients with advanced pancreatic cancer.

2. 5-Fluorouracil

5-FU has historically been a mainstay of treatment for patients with metastatic pancreatic cancer. Enthusiasm for the use of 5-FU in metastatic pancreatic cancer has been tempered by the fact that the response rates associated with its use are low. Response rates in the 20% range have been reported in older trials; however, the response rates associated with 5-FU given in combination with leucovorin in two more recent Phase II studies were < 10% [2,3].

Newer, oral 5-FU analogues have also demonstrated only modest activity in pancreatic cancer. Capecitabine, an oral precursor of 5-FU, is converted to 5-FU by an enzyme (thymidine phosphorylase) that is preferentially expressed in malignant cells [4]. A recent study involving 42 patients with advanced pancreatic cancer showed that treatment with capecitabine was associated with an overall response rate of 9.5% [5]. In another study, investigators from the Southwest Oncology Group treated 116 patients with eniluracil, an irreversible inactivator of dihydropyrimidine dehydrogenase, given in combination with oral 5-FU [6]. Responses were observed in only 8% of chemotherapy-naive patients and in 2% of pretreated patients. The median survival time for patients in this trial was only 3.6 months, leading the investigators to conclude that other treatment strategies are likely to hold more promise in the treatment of advanced pancreatic cancer.

3. 5-Fluorouracil-based chemotherapy combinations

Combination regimens based on 5-FU have failed to demonstrate significant survival benefits when compared to 5-FU monotherapy. A five-drug combination of 5-FU, cytoxan, methotrexate, vincristine and mitomycin C (the Mallinson regimen) was not associated with a significant survival advantage when compared in a randomised fashion to single-agent 5-FU [7]. Combinations of 5-FU, doxorubicin and mitomycin C (FAM) and 5-FU, doxorubicin and cisplatin (FAP) have also failed to demonstrate superiority to monotherapy with 5-FU in randomised trials [7,8]. In a recent, multi-centre European trial, > 200 patients with advanced pancreatic cancer were randomised to receive 5-FU with or without cisplatin. The 5-FU/cisplatin combination was associated with a response rate of 12%, as compared to a 0% response rate for single-agent 5-FU [9]. Despite the difference in response rates, no significant differences in survival were noted between the two arms. The use of protracted infusion 5-FU with or without mitomycin C has also been evaluated in a randomised trial of > 200 patients. The response rate associated with infusional 5-FU and mitomycin C was 20%, as compared to 8.3% for infusional 5-FU alone. Again, no significant differences in median survival were noted between the two arms (6.5 versus 5.1 months, $p = 0.42$) [10].

4. Gemcitabine

Recent years have witnessed the development of several new drugs for the treatment of pancreatic cancer, the most successful of which has been gemcitabine. Gemcitabine is a nucleoside analogue with structural similarities to cytarabine. Two initial Phase II studies demonstrated that gemcitabine was associated with modest activity in pancreatic cancer [11,12]. In a follow-up Phase II study, 74 patients with metastatic pancreatic cancer who were refractory to therapy with 5-FU were treated with gemcitabine [13]. Patients were followed not only for evidence of radiological response but also for evidence of clinical benefit, defined as reduction in pain intensity, decrease in analgesic use or improvement in performance status. In this trial, 27% of patients achieved a clinical benefit response, suggesting that a systematic assessment of subjective outcomes could be used to evaluate the impact of gemcitabine in patients with pancreatic cancer.

These studies led to a randomised trial, in which 126 patients with metastatic pancreatic cancer were randomised to receive either gemcitabine or 5-FU [1]. The primary end point in this trial was clinical benefit, as defined in the earlier Phase II study. Patients randomised to receive gemcitabine were treated using a regimen of gemcitabine 1000 mg/m^2 given over 30 min weekly for 7 weeks, followed by a 1-week rest period. Subsequently patients received gemcitabine weekly for 3 out of every 4 weeks. Patients randomised to the 5-FU arm received 5-FU 600 mg/m^2 weekly. This trial demonstrated that 23.8% of those patients receiving gemcitabine derived clinical benefit, as compared to only 4.8% of those who received 5-FU. The trial further demonstrated that treatment with gemcitabine was associated with improvements in both 1 year (18 versus 2%) and median survival times (5.65 versus 4.41 months). Based on the results of this trial, gemcitabine was approved as a standard first-line therapy for patients with metastatic pancreatic cancer in the US.

Subsequent studies with gemcitabine have focused on optimising its efficacy through modifications of both dose and infusion schedule. Gemcitabine is metabolised by deoxycytidine

kinase to several active metabolites that inhibit both DNA replication and repair. The rate of formation of these active metabolites is known to be dependent on dose rate. A recent randomised Phase II trial compared high-dose gemcitabine (2200 mg/m^2 given over the standard 30-min infusion) to fixed-dose rate infusion gemcitabine (1500 mg/m^2 given at a rate of 10 mg/m^2/min over 150 min) [14]. Patients in the fixed-dose rate infusion arm of this trial had superior objective response rates and superior 1- and 2-year survival rates compared to patients receiving high-dose gemcitabine, suggesting an advantage for the fixed-dose rate schedule.

5. Gemcitabine-based chemotherapy combinations

5.1 Gemcitabine/fluoropyrimidine combinations

The relatively mild toxicity profile of gemcitabine has allowed for the development of gemcitabine-based combination chemotherapy regimens, many of which have now been studied in patients with advanced pancreatic cancer. The activity of 5-FU in pancreatic cancer, albeit modest, led to early interest in gemcitabine/5-FU combinations. In one large, prospectively randomised trial performed by the Eastern Cooperative Oncology Group (ECOG), 327 patients with advanced pancreatic cancer received gemcitabine with or without weekly bolus 5-FU [15]. Patients in the single-agent arm of this trial received gemcitabine 1000 mg/m^2 weekly, administered for 3 out of every 4 weeks, whereas patients in the experimental arm received the same dose and schedule of gemcitabine together with 5-FU 600 mg/m^2. Patients receiving the gemcitabine/5-FU combination had a slightly longer median survival time than those receiving single-agent gemcitabine (6.7 versus 5.4 months); however, this difference was not statistically significant.

In an attempt to enhance the efficacy of the gemcitabine/5-FU combination, other investigators have combined weekly gemcitabine therapy with 5-FU administered as a prolonged intravenous infusion. In an initially encouraging Phase I/II study, 26 patients with metastatic pancreatic cancer received weekly gemcitabine in combination with infusional 5-FU administered at a dose of 200 mg/m^2/day [16]. The objective response rate in this trial was 19, and 42% of patients exhibited stabilisation of their disease. However, in a subsequent randomised Phase II study of 92 patients, weekly gemcitabine was compared to a regimen of weekly gemcitabine in combination with infusional 5-FU administered at a dose of 200 mg/m^2 for 6 of 8 weeks, followed by 3 of 4 weeks. The combination regimen was associated with an overall response rate of only 11%, as compared to 8% for gemcitabine monotherapy; and there was no difference in median survival time between the two arms [17]. These results again suggest that there is little, if any, advantage to adding 5-FU to gemcitabine in patients with advanced pancreatic cancer.

Combinations of capecitabine and gemcitabine also appear similar in efficacy to gemcitabine monotherapy, although data remain preliminary. In a Phase I/II trial, gemcitabine was given at a fixed dose of 1000 mg/m^2 on days 1 and 8 of a 21-day cycle and capecitabine was given in increasing doses for 14 days followed by a 1-week rest [18]. Objective radiological responses were noted in 5/27 (18.5%) patients treated with this regimen. Gemcitabine/capecitabine combination therapy has subsequently been compared to gemcitabine monotherapy in a randomised Phase II trial. A total of 83 patients with metastatic pancreatic cancer received either monotherapy with gemcitabine or a regimen of biweekly gemcitabine (2200 mg/m^2) in combination with capecitabine (2500 mg/m^2 given on days 1 – 7) [19]. The objective response rates observed with the two regimens were similar, with responses noted in 17% of the patients receiving combination therapy and 14% of patients receiving monotherapy. Phase III trials comparing gemcitabine monotherapy with gemcitabine/capecitabine combinations should better define the potential differences between these regimens.

5.2 Gemcitabine and cisplatin

Preclinical studies have suggested that gemcitabine may be synergistic with cisplatin as an inhibitor of DNA repair. This observation has led to several Phase II studies evaluating gemcitabine together with cisplatin in patients with metastatic pancreatic cancer (Table 1). In a German study, 41 patients with metastatic pancreatic cancer were treated with gemcitabine 1000 mg/m^2 (days 1, 8 and 15) in combination with cisplatin 50 mg/m^2 (days 1 and 15) [20]. In 35 evaluable patients, one complete response and three partial responses were observed, for an overall response rate of 11%. In a similar, 42-patient US study, 26% had complete or partial responses [21]. The most common toxicities in both studies were neutropenia and thrombocytopenia.

Using a slightly different dosing regimen, an Austrian group treated 16 patients with a combination of gemcitabine 1000 mg/m^2 and cisplatin 35 mg/m^2 given weekly for 3 out of every 4 weeks [19]. Objective responses were noted in 5/16 (31%) patients; however this regimen was associated with significant myelosuppression. To decrease the toxicities associated with this regimen, an Italian group modified the schedule and administered cisplatin 35 mg/m^2 in combination with gemcitabine 1000 mg/m^2 on days 1 and 8 of a 21-day schedule [22]. While this modified schedule was better tolerated, the results were disappointing, with objective responses noted in only 5/45 (9%) patients.

The most encouraging results with gemcitabine/cisplatin combinations have come from another Italian study, in which 107 patients with metastatic pancreatic cancer were randomised to receive either standard-dose gemcitabine or a combination of gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 administered 3 out of every 4 weeks [23]. The combination regimen was associated with an overall response rate of 26%, as compared to 0% among patients receiving single-agent gemcitabine. The median time to disease progression was also significantly longer in the patients receiving

Table 1. Phase II studies of gemcitabine 'doublet' combination chemotherapy in advanced pancreatic cancer.

No. patients	Response rate (%)	Median survival	Ref.
Gemcitabine/cisplatin			
45	9	5.6 months	Cascinu *et al.* [22]
42	26	7.1 months	Philip *et al.* [21]
41	11.5	8.2 months	Heinemann *et al.* [20]
16	31	9.6 months	Brodowicz *et al.* [19]
Gemcitabine/irinotecan			
60	25	7 months	Stathopoulos *et al.* [26]
45	24	5.7 months	Rocha-Lima *et al.* [27]
Gemcitabine/docetaxel			
34	8	8.9 months	Ryan *et al.* [58]
29	29	10.5 months	Jacobs *et al.* [32]
54	13	26 weeks	Stathopoulos *et al.* [59]
15	27	NA	Sherman *et al.* [60]
43	19	9 months	Ridwelski *et al.* [61]
33	9.4	4.7 months	ECOG [62]
14	7.1	6.1 months	Petrovic *et al.* [63]
24	17	6 months	Gonzalez *et al.* [54]
Gemcitabine/oxaliplatin			
30 (Stage II/ III patients)	31	11.5 months	Louvet *et al.* [34]
34 (Stage IV patients)	30.3	8.7 months	Louvet *et al.* [34]

ECOG: Eastern Cooperative Oncology Group; NA: Not available.

combination therapy (20 versus 8 weeks, p = 0.048). While no statistically significant survival differences were noted, the relatively small size of the study precluded a meaningful survival analysis. The superior response rate and time to disease progression associated with the gemcitabine/cisplatin combination in this study clearly warrant further confirmatory randomised studies.

5.3 Gemcitabine and irinotecan

Irinotecan is a topoisomerase inhibitor with demonstrated activity in several gastrointestinal malignancies. An initial Japanese trial of 35 patients demonstrated that single-agent irinotecan was associated with a response rate of 11% in patients with metastatic pancreatic cancer [24]. A subsequent Phase II trial confirmed these findings, demonstrating an overall response rate of 9% in 34 patients [25]. This evidence of activity, together with preclinical data suggesting synergism between irinotecan and gemcitabine, led to the investigation of combination regimens of gemcitabine and irinotecan.

In an initial study, the Greek Cooperative Group for Pancreatic Cancer treated 60 patients with gemcitabine 1000 mg/m^2 on days 1 and 8, in combination with irinotecan 300 mg/m^2 on day 8. Objective responses were noted in 25% of patients and the median survival time was 7 months [26]. One drawback to this regimen was a high incidence of neutropenia and the consequent requirement for growth factor support. In a second Phase II study, 45 patients with advanced pancreatic cancer were treated with a combination of gemcitabine 1000 mg/m^2 and irinotecan 100 mg/m^2 [27]. A total of 11 (24%) patients experienced partial radiological responses and 22 (50%) experienced declines in CA19-9 levels of > 50%. This regimen appeared to be well-tolerated: only 2% of patients experienced grade 4 neutropenia, 2% experienced grade 4 vomiting and 7% experienced grade 4 diarrhoea. Based on the promising results of this trial, this combination of irinotecan and gemcitabine is being compared to single-agent gemcitabine in a multi-centre Phase III randomised trial.

5.4 Gemcitabine and docetaxel

Docetaxel is a semisynthetic taxane that has been shown to have single-agent activity both in pancreatic cancer and in other malignancies. Phase II studies of single-agent docetaxel in patients with advanced pancreatic cancer have demonstrated overall response rates in the range of 0 – 20% [28-31]. Numerous Phase II studies of docetaxel in combination with gemcitabine have now been completed in patients with metastatic pancreatic cancer (Table 1). In one of the largest of these studies, 54 patients were treated with gemcitabine 1000 mg/m^2 (days 1 and 8) and docetaxel 100 mg/m^2 (day 8) on a 21-day schedule. Despite the use of prophylactic growth factor support, 11% of patients treated on this study developed febrile neutropenia, preventing the further development of this regimen. In a second study, patients were treated with gemcitabine 800 mg/m^2 (days 1, 8 and 15) and docetaxel 7 5mg/m^2 (day 1) on a 28-day schedule [32]. This dose schedule was also associated with excessive haematological toxicity and was subsequently changed to gemcitabine 1000 mg/m^2 and docetaxel 40 mg/m^2 administered on days 1 and 8 of a 21-day schedule, which was significantly better tolerated. Overall, 10/34 (29%) of patients had objective partial responses, supporting the further investigation of this gemcitabine/docetaxel regimen.

5.5 Gemcitabine and oxaliplatin

Oxaliplatin, a platinum analogue with structural similarities to cisplatin, differs from cisplatin in that it is not associated with significant renal toxicity. Oxaliplatin has also demonstrated promising activity in patients with metastatic colorectal cancer and was recently approved in the US for this indication. Evidence of possible synergism between oxaliplatin and gemcitabine has led investigators to explore gemcitabine/oxaliplatin combinations in patients with advanced pancreatic cancer. The North Central Cancer Treatment Group (NCCTG) performed a Phase I dose escalation study of gemcitabine in combination with oxaliplatin in patients with advanced pancreatic cancer, in which they identified a maximum tolerated dose of oxaliplatin 100 mg/m^2 administered on day 1 and gemcitabine 1000 mg/m^2 administered on days 1 and 8 of a 21-day

cycle [33]. In this trial, 3/18 (16%) patients demonstrated objective responses. In a recent Phase II study, 64 patients (34 with metastatic and 30 with locally advanced disease) were treated with gemcitabine 1000 mg/m^2 on day 1 and oxaliplatin 100 mg/m^2 on day 2 every other week [34]. The response rates associated with this combination were 31% for patients with locally advanced disease and 30% for patients with metastatic disease, and the median survival times were 11.5 months and 8.7 months, respectively.

5.6 Multi-drug gemcitabine-based combination regimens

The role of multi-drug gemcitabine-based combination regimens in the treatment of pancreatic cancer remains controversial. A three-drug combination of gemcitabine, cisplatin and infusional 5-FU, was associated with an objective response rate of 13% and a median survival time of 8.4 months [35]. Another regimen, utilising gemcitabine, 5-FU, leucovorin and cisplatin (G-FLIP) was associated with an objective response rate of 24% and median survival time of 3.9 months in patients refractory to first-line therapy [36]. Similar results were seen with a regimen utilising a combination of gemcitabine, oxaliplatin, leucovorin and infusional 5-FU [37]. While this regimen was associated with an encouraging overall response rate of 29%, grade 3 or 4 neutropenia occurred in 28% of cycles and febrile neutropenia developed during 5% of the treatment cycles.

In one of the most aggressive studies performed to date, an Italian group evaluated a four-drug combination of cisplatin, epirubicin, 5-FU and gemcitabine in 49 patients with unresectable pancreatic cancer [38]. Patients in this study were treated with 40 mg/m^2 each of cisplatin and epirubicin on day 1, gemcitabine 600 mg/m^2 on days 1 and 8 every 4 weeks and fluorouracil 200 mg/m^2/day as a protracted intravenous infusion. The regimen was associated with an impressive objective response rate of 58% and a median survival time of 11 months. Like many of the other multi-drug combinations, however, it was also associated with relatively high rates of neutropenia and thrombocytopenia. The toxicity associated with these multi-drug regimens, together with the often marginal performance status of patients with advanced pancreatic cancer, may preclude their widespread acceptance.

5.7 Future studies with gemcitabine-based combination therapy

The relatively small size of the many Phase II studies evaluating gemcitabine-based combinations makes it virtually impossible to assess which combination may be more promising than another and which, if any, may prove to be superior to gemcitabine monotherapy. Indeed, the superior response rates and encouraging median survival times observed in these studies may be explained simply by differences in patient selection. Several ongoing, randomised studies, in which these regimens are being compared both to each other and to gemcitabine monotherapy, should help resolve some of these questions. One such study, being performed by the Cancer and Leukaemia Group B (CALGB), randomises patients to receive either gemcitabine, administered at a fixed dose rate of 10 mg/m^2/min over 150 min or gemcitabine in combination with irinotecan, cisplatin or docetaxel (Figure 1). A second study, being performed by the ECOG, will randomise patients to receive standard dose gemcitabine, fixed dose rate gemcitabine or a combination of gemcitabine and oxaliplatin. The results of these studies, together with other large, prospectively randomised trials, are likely to define what future role gemcitabine-based combination therapy may play in the treatment of metastatic pancreatic cancer.

6. Novel agents in advanced pancreatic cancer

The development of novel agents provides additional hope for the future treatment of pancreatic cancer. The mechanisms of many of these new drugs differ significantly from standard cytotoxic agents, allowing them to be safely combined with more traditional regimens. Many, in fact, have already been evaluated in early clinical trials. While the results of some of these trials have been disappointing, other agents appear to be active in pancreatic cancer, both alone and in combination with more traditional agents.

6.1 Metalloproteinase inhibitors

Metalloproteinase inhibitors represent a class of proteolytic enzymes that are important in maintaining the extracellular matrix. It is thought that excess metalloproteinase activity may lead to breakdown of the extracellular matrix, tumour invasion and the development of metastases. One of the best studied of the metalloproteinase inhibitors is marimistat. A Phase III study performed in > 400 patients with metastatic pancreatic cancer compared marimistat, given at three different dose levels, to single-agent therapy with gemcitabine [39]. Gemcitabine was associated with an objective response rate of 26%, compared to only 3% for all three marimistat arms. Patients treated with gemcitabine also had a longer progression-free survival time than patients treated with marimistat, although no statistically significant differences in overall survival were observed. Given these negative results, it is unclear what role marimistat will play in the future treatment of pancreatic cancer.

6.2 Farnesyl transferase inhibitors

One of the most potentially attractive targets in the treatment of pancreatic cancer is the *ras* oncogene, which is mutated in > 90% of pancreatic carcinomas. Farnesyl transferase inhibitors (FTIs), prevent activation of the mutant Ras protein by blocking a key step in protein processing. While FTIs have shown promising activity in laboratory models, clinical trials of FTIs have, to date, been disappointing. In a Phase II study of the FTI R115777, involving 20 patients with metastatic pancreatic cancer, none responded to treatment [40]. Furthermore, a Phase III trial in which patients were randomised to

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