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Review paper

The role of gemcitabine alone and in combination in the treatment of pancreatic cancer

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Pancreatic cancer, one of the most frequently reported gastrointestinal tumors, has a 5-year survival of less than 5%. Despite representing only 2–3% of the total cancer incidence, it is the fifth leading cause of cancer death. This is because it is commonly only diagnosed at an advanced stage. Until recently the traditional therapy for patients with advanced disease was palliative 5-fluorouracil (5-FU)-based chemotherapy. However, the novel antinucleoside gemcitabine (Gemzar®) has demonstrated a survival benefit over 5-FU, and an improvement in disease-related symptoms and quality of life in patients with advanced disease. This review presents an overview of the clinical studies of gemcitabine, either alone or in combination, with other chemotherapeutic agents and/or radiation therapy, in the treatment of these patients. A comparison of these studies is made with those using alternative treatment regimens. The data suggest that gemcitabine in combination with biomodulated 5-FU should be considered the standard palliative treatment to which other new drug combinations or combined modality chemo-radiation regimens should be compared. [© 2000 Lippincott Williams & Wilkins.]

Key words: Combination treatment, gemcitabine, pancreatic cancer.

Introduction

Pancreatic cancer is the fifth leading cause of cancer death with age-adjusted yearly incidence rates of 5–10/100 000/year in the US and Europe.[1] Patients with locally advanced or viscerally involved pancreatic cancer have a poor prognosis and suffer debilitating disease-related symptoms. Disease progression is associated with pain in more than 75% of patients, anorexia in 64% and nausea in 50%, as well as weakness, impaired performance status and depression.[2,3] Less than 15% of newly diagnosed patients will survive 1-year and less than 5% will survive 5 years.[4,5]

For localized tumors surgery provides the only chance of a cure. The addition of post-operative radiotherapy predictably improves local control, but has only a minimal effect on survival. However, over 80% of patients with pancreatic cancer already have non-resectable tumors at the time of diagnosis.[6] The response rates achieved in these patients using conventional radiotherapy and chemotherapy strategies remain poor.[7–10] Moreover, an extensive number of phase II studies have failed to identify any chemotherapy regimen that has had a major impact on survival.[11]

The most extensively studied agent to date has been 5-fluorouracil (5-FU), with or without folinic acid (FA), but response rates have rarely exceeded 20% with no consistent effect on either disease-related symptoms or survival.[12–14] It is now generally accepted that the response rate with 5-FU is likely to be below 10% with very little impact on quality of life or survival.[15] Furthermore, the results obtained with 5-FU combination regimens were no better than those obtained with 5-FU alone and were associated with much greater toxicity.[16–19] In fact, it is only recently that the analysis of clinical benefit endpoints has suggested that chemotherapy might have a worthwhile role to play in the treatment of patients with advanced pancreatic cancer.[20]

xThe disappointing results obtained with 5-FU and 5-FU combination regimens only served to underline the need for new more effective agents for the treatment of advanced disease. Of the newer agents only paclitaxel (Taxol®), docetaxel (Taxotere®), topotecan, irinotecan, ZD 1694 (Tomudex®) and temozolomide have shown any kind of activity, with response rates of 5–17% in phase II studies.[21–27] However, the novel nucleoside analog gemcitabine (Gemzar®), despite its

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relatively modest response rates, has shown promising activity in the first- and second-line treatment of patients with advanced pancreatic cancer in four different trials in terms of disease stabilization, clinical benefit response (CBR) and survival.[28–31] The first of these was a US phase II study of 44 patients with advanced pancreatic cancer, in which gemcitabine not only achieved an objective response rate (RR) of 11%, a median survival of 5.6 months and a relatively high 1-year survival (23%), but also a positive effect on tumor-related symptoms.[28] In a European study of 34 patients, a RR of 6.3% and a median survival of 6.3 months were achieved, again coupled to an improvement in disease-related symptoms.[29] As a result, two controlled registration trials were designed to specifically evaluate the effect of gemcitabine on disease-related symptoms.[30,31] The first of these was a phase II study in 63 patients with 5-FU refractory pancreatic cancer. Seventeen patients (27%) achieved a CBR with a median duration of 14 weeks,[30] demonstrating a lack of cross-resistance between 5-FU and gemcitabine. In the second, a randomized study of single-agent gemcitabine versus single-agent 5-FU, gemcitabine proved itself to be superior to 5-FU in the treatment of patients with advanced pancreatic cancer.[31] Patients treated with gemcitabine had a significantly better CBR, derived from measurement of pain, functional impairment and weight loss, than those treated with 5-FU (23.8 versus 4.8%).[31] Disease stabilization was seen in 39 and 19% of the gemcitabine- and 5-FU-treated patients, respectively. The recent publication of the data from the Investigational New Drug program for the use of gemcitabine in the palliative treatment of pancreatic cancer[32] has provided evidence of notable disease-related symptom improvement (DRSI), 18.4% in 2471 patients. Although the criteria employed to measure the DRSI were not identical to those used to assess CBR, the data were consistent with those obtained previously for gemcitabine monotherapy. Survival data were evaluable for 2380 patients, and median survivals of 5.1 and 3.9 months were reported for chemonaive and previously treated patients, respectively. More recently, single-agent gemcitabine has been investigated in the locoregional treatment of patients with advanced pancreatic cancer with encouraging results.[33]

The novel mechanism of action, mild toxicity profile and therapeutic efficacy of gemcitabine coupled with its lack of cross-resistance with 5-FU in a clinical setting[31] make it an obvious partner for combination therapy with 5-FU, other antitumor agents and radiation therapy in the treatment of patients with advanced pancreatic cancer. Gemcitabine is currently the most extensively studied new agent in the treatment of pancreatic cancer and is currently becoming the 'therapy of choice' in a large number of treatment centers world-wide.

Gemcitabine in combination with other cytotoxic drugs

Gemcitabine and 5-FU

Due to the established single-agent activity of both gemcitabine and 5-FU in the treatment of pancreatic cancer, both agents may act as partners in combination therapy schedules. Gemcitabine and 5-FU act in different ways to inhibit DNA and RNA synthesis. Furthermore, gemcitabine inhibits the enzyme ribonucleotide reductase, which could lead to an increase in 5-FU activity.[34] Despite this, the two agents exhibit slightly different toxicity profiles.

To date there are 22 published reports of phase I–II studies of gemcitabine used in combination with 5-FU with or without FA for the treatment of patients with advanced pancreatic cancer (Tables 1 and 2), including one in which oxaliplatin was added to the combination.[35–56] Although the dose and schedule of administration of gemcitabine has been similar in nearly all the studies, the administration of 5-FU has varied from protracted continuous infusion to 24-h continuous infusion to weekly bolus at a variety of doses without[35–45] or with[46–54] FA. In the four completed studies,[35,41,42,46] which includes the authors' phase I study,[46] four different treatment schedules were used.

All trials report complete and/or partial responses, high incidences of disease stabilization, and for 13 of the studies median overall survivals in the range 5.25-13 months.[35,37–39,41–44,47,49,51–53] Both the response and the survival data are better than those achieved for either gemcitabine monotherapy[28–31] or 5-FU-based therapy alone[12–14] and clearly indicate the activity of this combination in the treatment of advanced disease.

Gemcitabine with infusional 5-FU. Hidalgo *et al.*[35] have completed a phase I–II study using bolus gemcitabine and continuous infusion 5-FU in 26 patients with advanced pancreatic cancer. Patients received gemcitabine 700–1000 mg/m^2 as a 30-min i.v. infusion weekly for three consecutive weeks out of four. 5-FU was administered as a protracted venous infusion (PVI) at a fixed dose of 200 mg/m^2/day in the absence of FA. A RR of 19.2%, including one complete response (CR) and four partial responses (PR), was achieved. Eleven patients (42.3%) achieved disease stabilization and the 1-year survival rate for this study was 39%. The median progression-free survival (PFS)

and overall survival times were 7.4 and 10.3 months, respectively. Furthermore, 45% of patients reported an improvement in disease-related symptoms. Neutropenia was the major dose-limiting toxicity in this study. Grade 3 neutropenia was observed in 16 out of 26 patients (61.5%) and grade 4 in three out of 26 patients (11.5%). A total of three out of 26 patients experienced grade 3/4 thrombocytopenia. The non-hematological toxicities were mild to moderate, with 11 patients displaying cutaneous toxicity. In nine patients this was typical of that observed with 5-FU delivered by PVI. Overall this regimen was adequately tolerated for up to six cycles (as per the protocol) and the authors recommended that a gemcitabine dose of 900 mg/m^2 was employed in further studies using this schedule. Several ongoing studies using the same regimen with fixed-dose gemcitabine (1000 mg/m^2) have been reported. To date, Borner *et al.*[36] have achieved a 25% overall RR in 12 assessable patients after two cycles of therapy. Minor responses were also recorded in 25% of patients. Hematological toxicities included WHO grade 3 thrombocytopenia (three patients) and leukopenia (five patients). Anchisi *et al.*[37] altered this regimen to gemcitabine 1000 mg/m^2 days 1 and 8 with 5-FU 200 mg/m^2/day continuous infusion days 1 through 15 every 21. Eighteen patients with advanced pancreatic cancer have been included so far. Comparable WHO grade 3 toxicities, including leukopenia (two patients), granulocytopenia (six patients) and thrombocytopenia (one patient) were observed. Out of 16 assessable patients, an overall RR of 25% was achieved and the overall median survival was 21 weeks (5.25 months). Rodriquez-Lescure *et al.*[38] using a weekly 48-h continuous infusion of 5-FU (3000 mg/m^2) in combination with gemcitabine (800–1400 mg/m^2) for 3 out of every 4 weeks, reported an overall RR of 19% in 21 assessable patients, which included one CR. In addition a CBR was observed in 57% of patients. Two other recently presented studies (Table 1)[39,40] support the efficacy of this combination

Gemcitabine with bolus 5-FU. In the second completed study, including 54 patients, Cascinu *et al.*[41] administered gemcitabine at a dose of 1000 mg/m^2 i.v. for 30 min for three consecutive weeks out of every four and 5-FU as an i.v. bolus at a dose of 600 mg/m^2 on the same days as gemcitabine. Two patients achieved a PR and 34 (63%) achieved stable disease. A clinical benefit was achieved in 28 patients (51%). The median survival for all patients was 7 months. The toxicity profile for this regimen was milder than that of the infusional regimen observed by Hidalgo *et al.*[35] with no evidence of grade 3 and 4 toxicity.

In another completed study, Berlin *et al.*[42] achieved a 14% overall RR in 36 assessable patients. Using the same doses and schedule for gemcitabine/5-FU, the median survival for all patients was 4.4 months and the 1-year survival was 8.6%. Grade 3 or 4 hematologic toxicities included leukopenia in 19% of patients, thrombocytopenia in 22% and anemia in 11% of patients, respectively. In an ongoing trial, Pastorelli *et al.*[43] reported an overall RR of 13% and performance status improvement of 69.9% in 24 patients with advanced pancreatic cancer treated with the same dose and schedule of gemcitabine/5-FU as in the previous two studies. The overall median survival in these patients was 7.5 months. Grade 3 or 4 toxicity included anaemia (13%), thrombocytopenia (23%) and diarrhea (9%).

A slightly reduced dose of 5-FU (500 mg/m^2) was administered in another weekly gemcitabine/5-FU trial conducted by De Gusmão *et al.*[44] Out of 14 included patients, the authors observed six PRs (42.8%) and seven patients achieved a CBR. In this small series, no WHO grade 3 or 4 toxicities were observed. Moreover, the interim median overall survival was 13 months compared with only 7 and 4.4 months in the studies of Cascinu *et al.*[41] and Berlin *et al.*,[42] respectively. The ongoing study of Tarantini *et al.*[45] using escalating doses of both gemcitabine and 5-FU also achieved a PR in four patients and a high rate of CBR, but was associated with high levels of toxicity (Table 1).

Gemcitabine in combination with 5-FU and FA. The fourth published study represents a phase I dose-finding study by the authors of the present review.[46] A constant gemcitabine dose (1000 mg/m^2) was administered to 17 patients, six of whom received a 5-FU dose of 750 mg/m^2, eight of whom received a 5-FU dose of 1000 mg/m^2 and two of whom received a 5-FU dose of 1250 mg/m^2. All patients received 200 mg/m^2 FA. In this study, gemcitabine was administered as a 30 min i.v. infusion followed by 200 mg/m^2 FA administered over 2 h, on days 1, 8, 15 and 22 of a 42-day schedule. 5-FU was administered using a portable pump over 24 h on days 1, 8, 15 and 22 of the same 42-day schedule. This deviation from the more usual 4-week (28-day) schedule for gemcitabine was an attempt to increase the level of exposure to the drugs and also to improve the quality of life, by allowing patients 3 weeks (days 23–42) without therapy. In this phase I study of 17 patients, there was one PR and nine patients achieved stable disease lasting longer than 3 months. Thirteen patients recorded an improvement in Karnofsky performance status (KPS). The subsequent phase II study which employed a 5-FU dose of 750 mg/m^2 achieved disease

Table 1. Gemcitabine in combination with 5-FU without FA

Reference	Gemcitabine dose	Combination drug(s)/therapy	No.	RR/CBR	Survival	Toxicity (no. pts)
Gemcitabine with infusional 5-FU						
Hidalgo[35]	700–1000 mg/m^2 days 1, 8, 15 q 28 days	5-FU 200 mg/m^2/day CI	26	19.2%/45%	10.3 months	grade 3 and 4 neutropenia in 16 and three patients, respectively; grade 3 and 4 thrombocytopenia in one and two patients, respectively
Borner[36]	1000 mg/m^2 days 1, 8, 15 q 28 days	5-FU 200 mg/m^2/day CI	12	25%	not available	grade 3 stomatitis (1), asthenia (1), leukopenia (5) and thrombocytopenia (3)
Anchisi[37]	1000 mg/m^2 days 1 and 8	CI 200 mg/m^2 day 1–15 q 3 weeks	19 (16)	4 PR (25%) 1 SD	5.25 months	–
Rodriguez-Lescure[38]	800–1400 mg/m^2 days 1, 8, 15 q 28 days	5-FU 3000 mg/m^2 (48 h CI) days 1, 8, 15 q 28 days	21	19%/57%	22 weeks	grade 4 neutropenia in two patients, grade 3/4 thrombocytopenia in one patient, diarrhea in one patient and mucositis in three patients
Shulman[49]	600 mg/m^2 days 1, 8, 15 q 28 days	200 mg/m^2/day CI for 21 days	15	2 PR (13%)	8.0 months	grade 3 neutropenia 13%, thrombocytopenia 6.6%, mucositis 13%, diarrhea 6.6% and myocardial ischemia 6.6%
Riedel[40]	1000 mg/m^2 days 1, 8, 15 q 28 days	2000 mg/m^2 24 h days 1, 8, 15 q 28 days	15 (14)	2 PR (14%)	1-year survival 36%	no grade 3/4 toxicity
Gemcitabine with bolus 5-FU						
Cascinu[41]	1000 mg/m^2 days 1, 8, 15 q 28 days	5-FU 600 mg/m^2 days 1, 8, 15 q 28 days	54	3.7%/ 51%	7 months	no grade 3/4 hematological toxicity reported
Berlin[42]	1000 mg/m^2 days 1, 8, 15 q 28 days	5-FU 600 mg/m^2 days 1, 8, 15 q 28 days	36	14%	4.4 months	grade 3/4 leucopenia (7), thrombocytopenia (8), anaemia (4), nausea (3) and vomiting (3)
Pastorelli[43]	1000 mg/m^2 days 1, 8, 15 q 28 days	600 mg/m^2 days 1, 8, 15 q 28 days	24	3 PR (13%)	7.5 months	grade 3 anemia, 13% and grade 3/4 thrombocytopenia 23%
De Gusmao[44]	1000 mg/m^2 days 1, 8, 15 q 28 days	5-FU 500 mg/m^2 days 1, 8, 15 q 28 days	14	42.8%/50%	13 months	no grade 3/4 toxicity observed
Tarantini[45]	I 1000 mg/m^2 II 1000 mg/m^2 III 1200 mg/m^2 days 1, 8, 15 q 28 days	I 1000 mg/m^2 bolus II 2000 mg/m^2 24 h III 2250 mg/m^2 24 h days 1, 8, 15 28 days 5-FU	17 14 I,II 3 III	4 PR/ [2 in I 1 in II 1 in III] 10/17 CBR	–	step II: neutropenia 12% anemia 6% and AST/ALT 6%

CI, continuous infusion.

stabilization in 89% of patients, a median time to progression (TTP) of 7.1 months and a median overall survival of 9.3 months.[47] The toxicity profile of this combination and schedule was extremely mild and eight patients progressing on this regimen went on to receive second-line paclitaxel therapy.

A total of six other studies have been reported of gemcitabine in combination with biomodulated 5-FU, i.e. 5-FU with FA (Table 2). These include the study of Polyzos *et al.*[48] which recorded a CBR in 50% of patients, disease stabilization in 37.5% of patients and a RR of 20%, in an ongoing 40 patient study using a

Table 2. Gemcitabine in combination with 5-FU and FA

Reference	Gemcitabine dose	Combination drug(s)/therapy	No.	RR/CBR	Survival	Toxicity
Oettle[47]	1000 mg/m^2 days 1, 8, 15, 22 q 28 days	5-FU 750 mg/m^2 24 h CI and FA 200 mg/m^2 2 h infusion days 1, 8, 15, 22 q 42 days	38	SD>3 months 89%	9.3+ months	<5% grade 3/4 toxicity
Polyzos[48]	750 mg/m^2 days 1 and 8 q 28 days	5-FU 350 mg/m^2 and leucovorin 350 mg/m^2 days 1, 2, 3, 7, 8 q 28 days	40	20%/50%	not available	no grade 3/4 toxicities reported
Louvet[49]	1000–1500 mg/m^2 day 3 q 14 days	5-FU 400 mg/m^2 bolus; 2000 or 3000 mg/m^2 48 h infusion q 14 days; leucovorin 400 mg/m^2 2 h infusion q 14 days	48	19.1%/50%	8 months	grade 3/4 neutropenia in 22.6% of cycles, thrombocytopenia in 6%, mucositis in 6% and diarrhea in 2.5%
Mousseau[50]	800 mg/m^2 day 3 q 21 days	5-FU 400 mg/m^2 bolus; 2000 mg/m^2 48 h infusion q 21 days; leucovorin 400 mg/m^2 2 h infusion day 1 q 21 days; oxaliplatin 85 mg/m^2 day 3 q 21 days	24	35%/74%	9 months	grade 3/4 toxicity included neutropenia (27% of cycles), thrombocytopenia (8% of cycles), diarrhea (3% of cycles) and nausea (10% of cycles)
Gutzler[51]	1000 mg/m^2 days 1, 8, 15 q 28 days	5-FU 100–500 mg/m^2 and FA 20 mg/m^2 days 1–5 q 28 days	12	8.3%	8.35 months	no grade 4 toxicities; grade 3 nausea/vomiting and diarrhea in three patients
Jovtis[52]	1000 mg/m^2 days 1, 8, 15	5-FU 600 mg/m^2 bolus; leucovorin 25 mg/m^2 days 1, 8, 15	18	4 PR	11 months	hematological 11.2%
Castellano[53]	1250 mg/m^2 day 1 or 3	5-FU 400 mg/m^2 bolus+600 mg/m^2 CI days 1 and 2 every 2 weeks	22	5 PR (19.3%)	8.8 months	no grade 3/4 toxicity if gemcitabine administered before 5-FU–FA
Lencioni[54]	1000 mg/m^2 days 1, 8, 15 q 28 days	5-FU 1400–2600 mg/m^2 24 h CI and leucovorin 250 mg/m^2 i.v. days 1, 8, 15 q 28 days	21	9.5%	not available	grade 3/4 neutropenia occurred in four of nine patients at the first dose level for 5-FU
Gemcitabine with oral fluoropyrimidines						
Herrmann[55]	1000 mg/m^2 days 1 and 8 q 21 days	capecitabine 1000–1600 oral daily	18	33%	not available	phase I: DLT neutropenia/ thrombocytopenia IV 10–33%
De Castro[56]	1000 mg/m^2 days 1 and 8, 15 q 28 days	UFT–leucovorin 250 mg/m^2 – 120 min d1 oral for 14 days ILV 7.5 mg/ 12 h UFT 390 mg/m^2/day	38	16% SD 39%	not available	diarrhea 17%, nausea/ vomiting 8% and neutropenia 5%

lower dose gemcitabine/5-FU–FA combination regimen (Table 2). In this study gemcitabine was administered at a dose of 750 mg/m^2, weekly for 3 out of 4 weeks, and 5-FU (350 mg/m^2) and FA (350 mg/m^2) were administered on days 1, 2, 3 and 7 of the same 4-week cycle. There were no grade 3 or 4 toxicities reported.

Louvet *et al.*[49] used a modification of the de Gramont LV5FU2 schedule FOLFUGEM, which included a 2-h i.v. infusion of 400 mg/m^2 FA followed by a 5-FU 400 mg/m^2 bolus and a 3000 mg/m^2 48-h infusion (first 24 patients) or a 2000 mg/m^2 bolus (remaining 24 patients). Gemcitabine was given on day 3 after 5-FU infusion at a dose of 1000 mg/m^2 (cycles 1 and 2) and raised to 1250 mg/m^2 (cycles 3 and 4). To date data are only available for the first 48 of the 63 patients entered into the study. An overall RR of 19.1% was achieved and a clinical benefit was observed in over 50% of symptomatic patients. The median TTP and overall survival were 4.5 and 8.0 months, respectively. Thirty-eight percent of patients were alive at 1 year. Grade 3–4 neutropenia was observed in 22.6% of cycles and grade 3–4 thrombocytopenia in 6.0% of cycles. There were three episodes of febrile neutropenia (1.2% of cycles). As a consequence of the treatment delays due to toxicity in 40.5% of treatment courses associated with this treatment schedule, the study is being continued with the exclusion of the 5-FU bolus and a reduced gemcitabine dose in an attempt to increase the gemcitabine 5-FU dose intensity.

Based on the results of the trial by Louvet *et al.*[49] Mousseau *et al.*[50] are conducting a study in patients with pancreatic cancer or carcinoma of unknown primary (CUP) using the FOLFUGEM regimen with a 21-day cycle and with the addition of oxaliplatin (FOLFU GEMOX Regimen). The schedule was the same as that used by Louvet and colleagues,[49] with reduced doses of 5-FU (2000 mg/m^2) and gemcitabine (800 mg/m^2). Oxaliplatin (85 mg/m^2) was administered on day 3 after the gemcitabine dose. Using this regimen, the overall RR was 35% including two CRs and four PRs in patients with pancreatic cancer. Seventy-four percent of patients achieved a CBR. Overall median survival was 9 months for patients with pancreatic cancer. Grade 3 or 4 toxicity (percent of cycles) included neutropenia (27%), thrombocytopenia (8%), diarrhea (3%) and nausea (10%).

Interim analysis of a phase I dose-finding study by Gutzler *et al.*[51] using a standard dose of gemcitabine (1000 mg/m^2) administered days 1, 8 and 15 of a 28-day cycle combined with fixed-dose FA (200 mg/m^2) administered days 1–5 and escalating doses of 5-FU (100–500 mg/m^2) given after gemcitabine days 1–5 recommended further use of gemcitabine plus 5-FU–FA in combination. Fifteen patients received at least six cycles of 28-day therapy. Dose escalation was stopped at 500 mg/m^2 5-FU due to hematological toxicity. Of the 12 patients followed for more than 4 months, one achieved a PR and five had stable disease. The median overall survival was 8.35 months. These data suggested that this combination of gemcitabine 5-FU–FA could be used in future studies at a 5-FU dose of 300 mg/m^2. Three more recent studies with 5-FU–FA[52–54] support the above observations about the efficacy of this combination. Castellano *et al.*[53] conducted a study to determine the most appropriate drug sequence with the gemcitabine, 5-FU and FA combination. The investigators compared a regimen in which gemcitabine (1250 mg/m^2) was given before 5-FU/FA on day 1 to a regimen in which gemcitabine was administered after 5-FU/FA on day 3. In both sequences, doses were comparable. An overall RR of 19.3%, an overall median survival of 8.5 months and a CBR of 50% was achieved in 26 assessable patients. According to the authors, the sequence with gemcitabine administered on day 3 (after 5-FU/FA) resulted in more toxicity than the alternate sequence (gemcitabine before 5-FU/FA).

Furthermore, two phase I–II studies containing combinations of gemcitabine with oral fluoropyrimidines, either capecitabine[55] or oral UFT in combination with FA,[56] have been published. Both show promising activity (including response rates of 16 and 33% in the smaller series) and an acceptable toxicity profile. So far, there are no survival data available.

The mean overall RR for 18 of the 22 studies listed in Tables 1 and 2 is 18.4% (range 3.7–42.8%; median 19%) for 449 patients. The median survival for 13 of the studies (Tables 1 and 2) is 8.0 months. To date, the regimen of De Gusmao *et al.*[44] represented by a study in only 14 patients is the most efficacious in terms of RR (42.8%), CBR (50%) and survival (13 months). Despite this, however, the data seem to suggest a slight advantage for the infusional or biomodulated, i.e. 5-FU/FA, schedules compared to bolus 5-FU in terms of median survival, 7.5[35,37–39,41–44] versus 8.8 months,[47,49,51–53] and toxicity (Tables 1 and 2). With regard to the infusional schedules without FA, it must also be borne in mind that most of them contain a period of long-term continuous infusion over several weeks. This represents a major compromise with regard to quality of life for these patients. With regard to toxicity, most trials report a lack of hematological toxicity exceeding 10% coupled with a lower rate of symptomatic toxicity.

All four of the completed studies,[35,41,42,45] irrespective of drug doses and schedule of administration, have

reported improved therapeutic outcomes compared with gemcitabine monotherapy,[28–31] 5-FU monotherapy[13] or biomodulated 5-FU therapy.[14] To date, several randomized phase III studies are under way, comparing toxicity rates and the efficacy of a combination schedule versus single-agent gemcitabine as the standard treatment for this patient group, with a view to confirming these phase II data.

Gemcitabine plus cisplatin and oxaliplatin

The single-agent activity of gemcitabine in the treatment of pancreatic cancer coupled to the known synergy between gemcitabine and cisplatin in preclinical studies[57] has led to the investigation of their activity in patients with advanced pancreatic cancer. The combination of gemcitabine and cisplatin has already been investigated in four phase II studies including one randomized study where gemcitabine plus cisplatin is compared with gemcitabine alone in a non-standard schedule (Table 3).

Heinemann *et al.*[58] reported an overall RR of 11.5%, a median TTP of 4.3 months and a median overall survival of 8.3 months in 35 out of 41 enrolled patients. Six patients had unresectable locally advanced disease and 35 metastatic pancreatic cancer. Gemcitabine (1000 mg/m^2) was administered days 1, 8 and 15 of a 28-day cycle and cisplatin on days 1 and 15 after gemcitabine. All treatment was essentially administered on an outpatient basis. Therapy was reported to be well tolerated, without any major compromises on quality of life. At a median number of 4.2 (range 1–11) cycles, grade 3 and 4 toxicities included neutropenia in 10 (29%) and two (6%) patients, thrombocytopenia in six (16%) and five (13%) patients, and anemia in five (13%) patients all grade 3. Disease stabilization lasting longer than 3 months was observed in 20 patients (57.1%). The 1-year survival was 28%. The patient who achieved a CR was still alive 26 months after study entry and six patients with stable disease were still alive at 12 months.

Using the same doses and schedule as above, Philip *et al.* achieved an overall RR of 36.4% (two CR and six PR) in 22 patients assessable for response.[59] The median survival for all 27 patients in this study was 7.4 months and the median TTP was 6.2 months. Again, as in the previous study, significant toxicity was observed and drug dosages were modified in the majority of patients. However, one has to conclude that this regimen had significant therapeutic activity.

Colucci *et al.*[60] in a randomized trial comparing gemcitabine alone (arm A) with gemcitabine plus cisplatin (arm B), using a different treatment schedule for the combination therapy, showed quite convincingly the advantages of the gemcitabine/cisplatin combination over gemcitabine alone. Gemcitabine (1000 mg/m^2) and gemcitabine (1000 mg/m^2) plus cisplatin (25 mg/m^2) were administered weekly for 7

Table 3. Gemcitabine in combination with cisplatin and oxaliplatin

Reference	Gemcitabine dose	Combination drug(s)/therapy	No.	RR/CBR	Survival	Toxicity
Heinemann[58]	1000 mg/m^2 days 1, 8, 15 q 28 days	Cisplatin 50 mg/m^2 days 1 and 15 q 28 days	35	11.5%	8.3 months	grade 3 and 4 neutropenia in 29 and 6%, thrombocytopenia in 16 and 13%, anemia in 13 and 0%, nausea/vomiting in 10 and 3%, alopecia in 3 and 0%
Philip[59]	1000 mg/m^2 days 1, 8, 15 q 28 days	Cisplatin 50 mg/m^2 days 1 and 15 q 28 days	27	36.4%	7.4 months	grade 3/4 neutropenia in 46%, thrombocytopenia in 54%, anemia in 42%, nausea/vomiting in 19%, nephrotoxicity in 8% and neuropathy in 8%
Colucci[60]	arm A and B: 1000 mg/m^2 weekly $\times$ 7, 1 week of rest, then 3 out of every 4 weeks	arm A: no concomitant drug; arm B: cisplatin 25 mg/m^2 following gemcitabine doses	A: 30 B: 32	A: 10% B: 31%/ A: 45% B: 38%	not available	grade 3/4 toxicity included neutropenia (13/26%), thrombocytopenia (3/3%), leukopenia (3/6%), anemia (3/6%), nausea/vomiting (3/3%) and diarrhea (0/3%)
Klapdor[61]	700 mg/m^2 30 min days 1 and 8 every 2 weeks	oxaliplatin 70 mg/m^2 in 4 h day 1	9	4 PR 2 MR	–	–

weeks, followed by 1 week of rest and then 3 weeks in every 4. Gemcitabine was administered in the combination arm on the fourth week of the first cycle only. The most recent report is that 103 patients have entered the study (arm A 51 and arm B 52). With 62 assessable patients (30 in arm A and 32 in Arm B), an overall RR of 10% has been reported for gemcitabine alone versus a 31% RR for gemcitabine plus cisplatin. In addition, 45% of patients in arm A and 38% in arm B obtained a CBR. Again more hematological toxicity was seen in patients receiving the combination regimen. So far, no survival or TTP data have been published for this study.

Klapdor *et al.*[61] have investigated gemcitabine in combination with oxaliplatin and have achieved four PRs and three stable diseases in a small series of nine patients. No survival or toxicity data are available for this study.

The OR for the three studies in which gemcitabine is combined with cisplatin (Table 3) is 26.3% with median survivals, where available, in excess of 7.4 months. These efficacy and survival data compare very favorably with the data obtained from the most recent study of cisplatin in combination with the previous standard therapy 5-FU, where the RR was only 12% and was also associated with high toxicity.[62] Toxicity in these combination regimens was significant but manageable. For those patients maintaining a good performance status, it could be concluded that gemcitabine and cisplatin in combination provided adequate palliative treatment for their pancreatic cancer.

Gemcitabine and docetaxel

The taxane docetaxel (Taxotere®) has proven activity in a variety of tumor types including carcinoma of the pancreas.[63,64] To date, six clinical trials have investigated gemcitabine in combination with docetaxel in the treatment of patients with advanced pancreatic cancer (Table 4).[65–70] The first study by Kakolyris *et al.*[65] in which gemcitabine (1000 mg/m^2) was administered days 1 and 8 in combination with doctaxel (100 mg/m^2) day 8 every 3 weeks, yielded an OR of 7.4% (two PRs out of 27) and stable disease in nine patients (33.3%). Overall, the median TTP was 7 months and the median survival 7 months. A CBR was observed in seven out of 16 patients (43.7%) who presented with disease-related symptoms. Thus, gemcitabine in combination with docetaxel using this regimen was deemed to have only marginal activity and to offer no advantage over single-agent therapy with either gemcitabine or docetaxel. Jacobs *et al.*,[66] in a phase II study of gemcitabine (800 mg/m^2) administered on days 1, 8 and 15 and docetaxel (75 mg/m^2) on day 1, reported seven PRs and 10 patients with stable diseases in 25 evaluable patients. The schedule was changed due to excessive hematological toxicity (Table 4) and to date a RR of 28% has been achieved in 25 evaluable patients. However, lower doses of gemcitabine (600 mg/m^2) and docetaxel (60 mg/m^2) using the same schedule led to a response rate of only 8% in another phase II trial including 24 patients.[67] Grade 3 or 4 toxicity included fatigue (four patients), diarrhea (three patients), nausea (two patients), and depression and neuropathy (one patient each). Febrile neutropenia was also reported in 22% of patients. In conclusion, this regimen does not appear to be better than either agent used alone.

Lueck *et al.*[68] in a phase I dose-finding study, initially with fixed-dose gemcitabine (800 mg/m^2) where docetaxel was escalated from 25 to 45 mg/m^2 on a weekly schedule, recommended a dose level of weekly gemcitabine, 1000 mg/m^2, and docetaxel, 35 mg/m^2 (Table 4). Thirteen patients have been evaluated in the phase II study to date, yielding a RR of 23% and disease stabilization in 69% of patients. No survival data are currently available. However, Cascinu *et al.*[69] in a phase I/II trial, determined the maximum tolerated dose (MTD) of docetaxel administered day 8, in combination with fixed-dose gemcitabine (1000 mg/m^2) administered days 1 and 8 every 3 weeks, to be 70 mg/m^2. Administration of this dose of docetaxel in the above schedule to 18 patients in a phase II study resulted in one PR, a TTP of 3 months and a median treatment survival of 5.4 months. Once more, the authors of this study[69] concluded that the addition of docetaxel to gemcitabine in the treatment of advanced pancreatic cancer was not particularly useful. The controversy surrounding docetaxel continues with the publication of the recent trial by Androulakis *et al.*[70] in which gemcitabine (1000 mg/m^2) was administered on days 1 and 8 and docetaxel (100 mg/m^2) on day 8 of a 21-day schedule. This trial presented better response and survival data (Table 4), but again was associated with high levels of toxicity. These results coupled with the ongoing controversy surrounding the efficacy of docetaxel as a single agent in the treatment of these patients[71,72] suggest that docetaxel is unlikely to be a favored combination partner for gemcitabine. Furthermore, this combination is associated with increased therapy costs.

Other combination regimens with gemcitabine

The success of gemcitabine as a monotherapy in the treatment of patients with pancreatic tumors coupled

Table 4. Gemcitabine in combination with docetaxel

Reference	Gemcitabine dose	Combination drug(s)/ therapy	No.	RR/CBR	Survival	Toxicity
Kakolyris[65]	1000 mg/m^2 days 1 and 8 q 21 days	docetaxel 100 mg/m^2 day 8 q 21 days	27	7.4%	7 months	grade 3/4 toxicity included neutropenia (0.5%), thrombocytopenia (7.9%) and diarrhea (5.2%)
Jacobs[66]	800 mg/m^2 days 1, 8, 15 q 28 days 1000 mg/m^2 days 1 and 8 q 21 days	docetaxel 75 mg/m^2 day 1 q 28 days docetaxel 40 mg/m^2 days 1 and 8 q 21 days	25	28%	not available	grade 3 hematological toxicity in four patients for first schedule
Clark[67]	600 mg/m^2 days 1, 8, 15 q 28 days	docetaxel 60 mg/m^2 day 1 q 28 days	24	8%	not available	grade 3 or 4 fatigue (4), diarrhea (3), nausea (2), depression (1) and neuropathy (1); 22% with febrile neutropenia
Lueck[68]	800 mg/m^2 weekly $\times$ 12 cycles; 1 week rest after cycles 6 and 9	docetaxel 25–45 mg/m^2 weekly $\times$ 12 cycles; 1 week of rest after cycles 6 and 9	13	23%	not available	grade 3/4 toxicity gastrointestinal was observed at these docetaxel dosage levels 40 and 45
Cascinu[69]	1000 mg/m^2 days 1 and 8 q 21 days	docetaxel 70 mg/m^2 day 8 q 21 days	18	5.5%	5.4 months	–
Androulakis[70]	1000 mg/m^2 days 1 and 8 q 21 days	docetaxel 100 mg/m^2 day 8	56	11.5%	8 months	grade 3 neutropenia (15; 23%), anemia (6; 10.7%), thrombocytopenia (4; 8%), fatigue (7; 13%) and diarrhea (2)

with its mild toxicity profile has inevitably lead to its combination with a variety of therapeutic agents. These include epirubicin,[73,74] mitomycin C,[75–77] octreotide,[78,79] tamoxifen,[80] marimastat,[81,82] capecitabine[83,84] and irinotecan,[85,86] as well as multi-drug regimens where gemcitabine has been combined with epirubicin, cisplatin and 5-FU.[87,88] The results of some of these studies are presented in Table 5. The last two combinations have provided extremely encouraging response rates, but no obvious improvement in survival. In one study[87] this was associated with considerable toxicity. Intra-arterial delivery of gemcitabine and mitomycin C has also yielded high response rates and encouraging survival data in a study with a small patient number,[77] but as yet there are no data available regarding grade 3 and 4 toxicity.

Recently, two Phase II studies have investigated the combination of gemcitabine and irinotecan (CPT-11) for the first-line treatment of advanced pancreatic cancer. Stathopoulos *et al.*[85] administered gemcitabine 900 mg/m^2 days 1 and 8 with irinotecan 300 mg/m^2 day 8 every 21 days to 28 chemonaive patients. In 20 assessable patients, three patients achieved PR (15%). The median survival was not reached at the time of publication. Grade 3 or 4 toxicity included neutropenia (36%), thrombocytopenia (8%), anemia (18%) and diarrhea (4.6%).

In the study by Rocha Lima *et al.*[86] gemcitabine 1000 mg/m^2 and irinotecan 100 mg/m^2 were both administered on days 1 and 8 every 21 days to 45 patients with advanced pancreatic cancer. A 20% overall RR was achieved with an overall median survival of 6 months. Grade 3 and 4 toxicity included neutropenia (13.3 and 2.2%), thrombocytopenia (6.7 and 2.2%), vomiting (2.2 and 2.2%) and diarrhea (6.7% and 0).

However, although some of these studies have yielded exciting RRs, there is no evidence that the increased toxicity associated with these regimens[87,88] can be translated into enhanced survival, when compared with the less toxic gemcitabine/5-FU combinations (Tables 1, 2 and 5).

Combined modality gemcitabine and radiation therapy

Adjuvant chemoradiation, as stated in the Introduction, has been shown to be superior to surgery alone in patients with potentially resectable pancreatic

Table 5. Some of the other combination regimens incorporating gemcitabine

Reference	Gemcitabine dose	Combination drug(s)/ therapy	No.	RR/CBR	Survival	Toxicity
Neri[73]	800–1000 mg/m^2 days 1, 8, 15 q 28	epirubicin 20 mg/m^2 days 1, 8, 15 q 28	12	25%/45%	not available	grade 3/4 granulocytopenia in two of four patients at 1000 mg/m^2 gemcitabine dose
Raderer[74]	1000 mg/m^2 days 1, 8, 15 q 35	epirubicin: 60 mg/m^2 day 1; G-CSF 5 μg/kg days 2–6 q 35	47	19%/40%	>5.5 months	grade 4 hematological toxicity in 18%
Bazin[75]	1000 mg/m^2 days 1, 8, 15 q 35	mitomycin C 5 mg/m^2 day 1 q 35	14	28.5%/ 46.6%	not available	grade 3/4 toxicities: neutropenia 45.2%; thrombocytopenia 54% and anemia 34.7%
Bazin[76]	1000 mg/m^2 days 1, 8, 15	mitomycin C 5–10 mg/m^2 day 1	16	38%/60%	–	neutropenia 45.2% thrombocytopenia 54% and pulmonary 20%
	1000 mg/m^2 days 1, 8, 21, 29	mitomycin C 8 mg/m^2 day 2	9			neutropenia 12.3% thrombocytopenia 4% pulmonary 1.9, flu syndrome 38% and edema 20%
Klapdor[77]	800 mg/m^2 via truncus catheter (intra-arterial) day 1 and 800 mg/m^2 i.v. days 8 and 15	mitomycin C 10–15 mg/m^2 via truncus catheter (intra-arterial) day 1	15	53%	>7 months	information not stated
Carmichael[82] Phase I	1000 mg/m^2	marimastat 2 × 20 mg days 5, 10, 15	31	2/11 (18%)	–	grade 4 bilirubin one patient; different grade 3 toxicities (including myelosuppression in nine patients)
Statho-poulos[85]	900 mg/m^2 days 1, 8 q 21 days	irinotecan 300 mg/m^2 day 8 q 21 days	20	15%	not available	grade 3 or 4 neutropenia (36%), thrombocytopenia (8%), anemia (18%) and diarrhea (4.6%)
Rocha Lima[86]	1000 mg/m^2 days 1 and 8 q 21 days	irinotecan 100 mg/m^2 days 1 and 8 q 21 days	45	20%	6 months	grade 3 and 4 neutropenia (13.3 and 2.2%), thrombocytopenia (6.7 and 2.2%), vomiting (2.2 and 2.2%) and diarrhea (6.7 and 0%)
Villa[87]	600 mg/m^2 days 1, 8 q 28 days	cisplatin and epirubicin 40 mg/m^2 days 1 q 28; 5-FU 200 mg/m^2/day continuous infusion	26	69%	>8 months	grade 3/4 toxicity (% of cycles) neutropenia (56%), thrombocytopenia (33%), anemia (8%), stomatitis (6%), diarrhea (3%) and nausea/vomiting (2%)
Reni[88]	600 mg/m^2 days 1 and 8	epirubicin+cisplatin 40 mg/m^2 day 1 5-FU 200 mg/24 h day 1 and 8	29	62%	6.5+ months	not stated

cancer. Also, although the majority of patients with advanced disease receive cytotoxic chemotherapy, with palliative intent, to relieve disease-related symptoms, unresectable, locally advanced tumors can be treated with radiotherapy alone or in combination with chemotherapy.[89] Combined modality therapy with radiotherapy and 5-FU-based chemotherapy (either alone or in combination with cisplatin or other agents) has shown these combinations to be feasible, and to provide favorable response and survival data.[90–94] The data have even lead to the suggestion that the duration of therapy could be reduced.[92] In fact a complete response has been reported to combined i.v. chemotherapy with 5-FU, mitomycin C, epirubicin,

oral UFT and cyclophosphamide, and intra-arterial cisplatin, 5-FU and epirubicin and radiotherapy.[95] It therefore seems reasonable to investigate gemcitabine as the new mainstay of pancreatic chemotherapy in combination with radiotherapy for the treatment of these patients with advanced pancreatic cancer for whom, even with treatment, survival past 2 years is uncommon.

Gemcitabine is a potent radiosensitizer,[96] possibly reducing the threshold for radiation-induced apoptosis. Phase I studies in locally advanced disease[97–99] and metastatic disease[100] have demonstrated that weekly or biweekly gemcitabine combined with radiotherapy is feasible with acceptable toxicity. More recently, a variety of studies of gemcitabine either alone or plus other chemotherapuetic agents, in combination with radiotherapy, have been reported[101–107] and are summarized in Table 6. Radiochemotherapy with gemcitabine and 5-FU preceded and followed by gemcitabine/cisplatin therapy has shown a downstaging in 70% of patients and the goal of resectability achieved in five out of 13 patients.[105] Gemcitabine/cisplatin alone have also been combined with radiation therapy.[106,107] Although there are no response data available for these studies, the preliminary data for one study in six patients using low-dose gemcitabine[107] suggest that this therapy is well tolerated. Combined modality therapy with gemcitabine, particularly the study of Antonisse *et al.*,[103] compares very favorably in terms of toxicity with other combined modality therapy combinations.[106–112] The ultimate goal will be to implement this regimen in resectable pancreatic cancer prior to surgery and post-surgery.[105,112] A phase I study of intra-arterial delivery has also shown encouraging results.[110]

Conclusion

Gemcitabine has proven activity in pancreatic cancer both as a single-agent and in combination with a variety of other chemotherapy agents, as the data presented in this review clearly indicate. Currently, the most experience and data have been accrued for gemcitabine in combination with 5-FU with or without FA. With this combination, RRs of 19–40% have been observed in non-randomized phase II studies as well as CBR in up to 50% of patients. However, Colucci *et al.*[60] observed more PRs (31 versus 10%) when the combination of gemcitabine and cisplatin was compared to gemcitabine alone. Additionally, objective responses and CBRs have been observed in other combination studies with gemcitabine (Tables 3 and 5). As a result, for most of the studies where survival data are available, combination chemotherapy with gemcitabine leads to a median survival of approximately 8–9 months. However, there is a considerable variation in toxicity across the different gemcitabine therapy combinations. Although the dose and schedule of administration of gemcitabine have been similar in nearly all the studies, different combination partners and schedules lead to different rates of toxicity. In our opinion, due to the disease-related performance status of the patients, palliative treatment schedules must not exceed WHO grade 3 toxicity levels. For this reason, gemcitabine administered in combination with biomodulated 5-FU seems to be the most favorable therapy option. It can be administered on an outpatient basis with scheduling that, e.g. in the case of the authors' own study, takes into account the patients quality of life needs. Although clearly some of the schedules of 5-FU administration are associated with greater toxicity than others, this combination, irrespective of the route of 5-FU administration, would seem to offer a therapeutic advantage over either agent administered as monotherapy. As this therapy is being administered with purely palliative intent, we can maybe learn a lesson from the treatment of colorectal malignancies, and not waste time searching for and perfecting the ideal method of 5-FU delivery, but choose the combination that offers efficacy in the absence of severe toxicity, whilst meeting the requirements of the specific treatment centres and regulatory authorities.

To date, most of the available data are only from ongoing non-randomized phase II trials which have been published in abstract form. The full publication of these data and additional phase II and III studies will be required to assess whether improved overall RR, CBR and survival are achieved with specific combination regimens over gemcitabine alone.

However, despite the encouraging RR data and improvement in survival reported in this review for gemcitabine in combination with other agents, particularly 5-FU and radiotherapy, the main reason for treatment failure remains disseminated metastatic disease. The natural history of pancreatic cancer, even in patients with the best prognosis, is one of apparently curative resection followed by the development of local recurrence and eventually liver metastases. Thus, any adjuvant or first-line therapy for patients with pancreatic cancer must be effective against local recurrence and systemic spread. At the present time the evidence suggests that gemcitabine in combination with biomodulated 5-FU should be the reference regimen against which other novel combinations are compared. The obvious new combination partners for gemcitabine in the treatment of advanced

Table 6. Gemcitabine in combination with radiation therapy

Reference	Radiation dose	Combination drug(s)/ therapy	No.	RR/CBR	Survival	Toxicity
Epelbaum[101] Phase II	total dose 50.4 Gy in 1.8 Gy fraction	gemcitabine 1000 mg/m^2 weekly for 7 weeks 400 mg/ m^2 weekly × 3 every 28 days for 2 cycles re-escalated after radiotherapy finish	20	4 PR 20% 6 MR 30% 2 NC 50% CBR	12 months	grade 3/4 nausea/vomiting /diarrhea in three patients; neutropenic fever in one patient
Antonisse[103]	3 fractions of 8 Gy/weekly days 1, 8, 15	300 mg/m^2 days 1, 8, 15 1000 mg/m^2 up to day 22	21	–	16.2 months	no
Reyes-Vidal[104]	4500 cGy in 25 fractions	200–350 mg/m^2 i.v. weekly 5 weeks	14	2 CR 6 PR	–	grade 3 neutropenia 1 patient, grade 3 anemia 1 patient, grade 4 diarrhea five of 13 patients
Wilkowski[105]	1.80 Gy per fraction total 45 Gy	gemcitabine 300 mg/ m^2 5-FU 350 mg/m^2 +gemcitabine cisplatin before or after chemotherapy	13	downstaging in 70% of patients, resectability achieved in five of 10 patients.		
Brunner[106]	SD 1.8 Gy daily TD 50.4 Gy down to 55.8 Gy	cisplatin 20 mg/m^2 days 1–5, 29–33 gemcitabine 600 mg/ m^2 days 2, 5, 12, 19, 26, 33, 40 days	10	one restaging with RO resection	–	leukopenia 7/10 grade 3; 2/ 10 grade 4; thrombocytopenia 3/10 grade 3; 4/10 grade 4; nausea, vomiting 3/10 grade 3; 0/10 grade 4
Mazin Safar[107]	4500 Gy in 25 fractions	100 mg/m^2 increased steps in 50 mg + cisplatin 20 mg/m^2	6	–	–	two patients grade 4 (thrombocytopenia) escalation to 150 mg/m^2 without problems
Brunner[108]	1.8 Gy total dose 50.4 Gy followed by a boost to 55.8 Gy	mitomycin C 10 mg/ m^2, i.v. bolus injection. day 2 and 30 + 5-FU 1000 mg/ m^2 i.v. as 120 h continuous infusion days 1–5 and 29–33	27	9/25 RO resection	median follow-up 20 months, six of 25 alive	grade 3/4 upper GI tract 5/27–0/27 grade 3/4 diarrhea 0/27 grade 3/4 leukopenia 6/27–1/27 grade 3/4 thrombopenia 1/27–1/27 grade 3/4 Hb 2/27–0/27
Berns[109]	44.8 Gy in 28 fractions (2 × 1.6 Gy)	FA 300 mg/m^2 days 1–3 5-FU 600 mg/m^2 days 1–3	90 62		12.8 months	grade 3/4 leuko/ thrombopenia 10% grade 3/4 nausea/vomiting 14.5% mucositis 7.2%
Osinsky[110]	5-FU 2–2.5 g/m^2 + ADR 50–60 mg/m^2 + cisplatin 40–50 mg/m^2 over 120 min days 1–4	3 days after chemotherapy 5 fractions (2.5 Gy) per week (total dose 30 Gy)	29	10 PR	TTP 11.3 months	leukopenia 8/29 nausea/ vomiting 12/29

disease include matrix metalloproteinases such as marimastat[81,82] and angiogenesis inhibitors,[113] both of which have been developed clinically to inhibit tumor spread. One could also envisage gemcitabine combinations being used in combination with antibody therapies, as an adjunct to prodrug-activated (suicide) gene therapy,[114] or in combination with intratumoral injections with p53.[115,116] Indeed, preclinical studies suggest that this approach could represent a promising approach for the treatment of pancreatic cancer patients. Thus, gemcitabine in combination with existing and novel new therapies clearly provides the hope for the future in the treatment of patients with pancreatic cancer.

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