J Hepatobiliary Pancreat Surg (2002) 9:61–75

Journal of HBP Surgery



# What's new in pancreatic cancer treatment?

Man C. Fung and Tohru Sakata

Oncology Department, Lilly Research Laboratories-Japan, Eli Lilly Japan, Sanomiya Plaza Building, 7-1-5 Isogamidori, Chuo-ku, Kobe 651-0086, Japan

**Abstract** Pancreatic cancer represents a major challenge to oncologists because of its high chemoresistant nature and dismal outcomes. Conventional therapy for advanced disease relied for a long time on palliative 5-fluorouracil (5-FU)-based chemotherapy, but with unsatisfactory results. The introduction of the novel antimetabolite gemcitabine provides new optimism for patients with advanced pancreatic cancer, as multiple clinical trials have demonstrated the superiority of gemcitabine over 5-FU and other agents for these patients. The benefits of gemcitabine over conventional therapies include improved response rate and enhanced survival, as well as improvement in disease-related symptoms and quality of life in these patients. With these data, gemcitabine is widely accepted worldwide as the therapy of choice by many oncologists for advanced pancreatic cancer. The current review presents an overview of the clinical studies of gemcitabine over the past decade for the treatment of patients with advanced pancreatic cancer. Other investigational regimens or uses (e.g., fixed dose-rate infusion, intraarterial infusion, adjuvant use, chemo-radiation, etc) are also reviewed.

**Key words** Adjuvant therapy · Chemotherapy · Clinical benefit response · Chemoradiation · Gemcitabine · Neoadjuvant therapy · Pancreatic cancer · Review

## Introduction

Pancreatic cancer accounts for approximately 2%–3% of all malignant neoplasms worldwide.[1–6] It causes around 200 000 deaths yearly and is the fifth most common cause of cancer mortality in the world. Pancreatic cancer is a major challenge to oncologists because of its high frequency of oncogene mutations and highly chemoresistant nature.[6,7] Disease progression is often associated with debilitating symptoms, such as abdominal and back pain, anorexia, weight loss, nausea, jaundice, fatigue, and depression. Unfortunately, because of the lack of early symptoms, most patients would present with advanced disease when diagnosed, and the outcome has generally been very poor. The median survival for patients with advanced disease is in the range of only a few months.[3–6]

Many chemotherapeutic agents were previously tested as single or combination therapies for pancreatic cancer.[8–19] However, the response rates have been highly variable, and are often unreproducible. Among these agents, fluorouracil (5-FU) perhaps was the most extensively studied.[12–19] However, the response rates of 5-FU were quite variable, as well as not showing a consistent benefit on either survival or improvement of symptoms. Other chemotherapy agents or combinations have also failed to demonstrate any improved response rates or survival compared with 5-FU.[16–19] Because of the lack of satisfactory treatment for advanced pancreatic cancer, there is a need for new oncolytic agents to be evaluated.

Gemcitabine is a pyrimidine antimetabolite that exhibits a broad range of activity against a variety of solid tumors.[20,21] Preclinical studies had demonstrated the activity of gemcitabine in the inhibition of human pancreatic cells in vitro. Over the past decade, multiple clinical studies have illustrated the benefits of gemcitabine for pancreatic cancer, especially in terms of disease stabilization, clinical benefit response (CBR), and survival. Since its first approval for use in the United States and Europe in the mid-1990s, gemcitabine has become the agent of choice for the treatment of advanced pancreatic cancer. The current report provides an overview of the published clinical data for the use of gemcitabine in pancreatic cancer.

*Offprint requests to:* M.C. Fung

Received: October 27, 2001 / Accepted: November 16, 2001

**Single-arm studies**

To date, there have been ten studies published using gemcitabine as a single agent for advanced pancreatic cancer.[22–32] These studies were published from 1994 to 2001. All studies used 800–1500 mg/m$^2$ of gemcitabine on a weekly basis, in either the conventional 4-week schedule (on days 1, 8, and 15) or the 7-week first regimen (continuously for 7 weeks with 1 week of rest, followed by the regular 4-week schedule). Table 1 depicts the details of these studies. As can be seen from the data presented, although the objective responses observed were relatively low (4.3% to 18.2%), there were a substantial number of patients with stable disease (18.8% to 50.0%). Excluding the study of Rothenberg et al.,[32] which was conducted in patients who failed prior 5-FU therapy, the median overall survival reported was 5.0 to 9.8 months, which was higher than the customary 3–6 months approximate survival for these patients without treatment. One-year survival was reported as being between 14.3% and 39.0%.

Interestingly, the investigators in these studies also noted that symptom improvement had occurred in patients not achieving an objective tumor response. This was an important observation, because many patients with advanced pancreatic cancers were symptomatic and experienced debilitating pain, severe anorexia, weight loss, and low performance status. This observation led to the use of the clinical benefit response (CBR) as an alternative outcome measurement to evaluate the efficacy of gemcitabine in pancreatic cancer. CBR is a measure of clinical improvement in terms of pain intensity, analgesic consumption, performance status, and weight change.[33,34] A patient will be considered a responder if rated "positive" for either of the primary measures of pain or performance status without a negative rating in the other parameters. A patient could also be a responder if both of the two primary parameters are stable and there is a weight gain. Among the studies reviewed, CBR was achieved in 26.6% to 48.0% of the patients.

Toxicities were generally modest and manageable, as few patients needed discontinuation of the therapies as a consequence. Among these studies, the grade 3–4 hematological toxicities observed were leukopenia (6.1%–27.3%), neutropenia (6.6%–36.4%), thrombocytopenia (0.0%–18.0%), and anemia (3.0%–22.0%), which were quite acceptable from the perspective of cytotoxic agents. In addition, the hematological toxicities were generally reversible over time or during the resting week and rarely led to significant infections, bleeding, or toxic deaths. Nonhematological toxicities were also modest, with nausea and vomiting, transaminase elevations, fever, and rash the most commonly reported.

One study perhaps worthy of further discussion was the one from Rothenberg et al.[32] This study investigated the use of gemcitabine in patients who failed prior 5-FU treatment. Of the 63 assessable patients, partial responses were seen in 10.5% of the patients, with an additional 29.8% who had stable disease. CBR was noted in 27% of the patients, and the median survival was 3.85 months. This study illustrated the utility of gemcitabine in 5-FU-failure patients and the lack of cross-resistance between these two agents.

**Randomized studies**

To date, eight randomized studies have been published comparing gemcitabine with either another chemotherapeutic agent or with a combination of another agent plus gemcitabine.[35–42] Table 2 depicts the details of these studies. The first, and perhaps the most discussed study, was the randomized phase III study by Burris et al.,[35] which substantiated the efficacy of gemcitabine noted in earlier studies, as well as demonstrating the advantage of gemcitabine over 5-FU as first-line treatment for patients with locally advanced or metastatic pancreatic cancer. In that study, 126 symptomatic patients were randomized to receive either gemcitabine (63 patients) or 5-FU (63 patients). The regimen of gemcitabine was 1000 mg/m$^2$, using the 7-week initial regimen, while patients on 5-FU received a dose of 600 mg/m$^2$ once weekly. There were 23.8% of the patients who achieved CBR in the gemcitabine arm compared with 4.8% for the 5-FU patients ($P = 0.0022$). Median survival was 5.65 months for the gemcitabine-treated patients compared with 4.41 months for those who received 5-FU ($P = 0.0025$). In addition, other efficacy parameters, such as median time to progressive disease (2.1 vs 0.9 months) and 1-year survival probability (18% vs 2%), were all more favorable for the gemcitabine-treated patients. Both treatments were well tolerated, despite a slightly higher incidence of hematologic events noted in the gemcitabine arm. Table 2 depicts the details of the comparison.

Three other randomized studies were completed comparing agents of newer therapeutic classes that were being developed for pancreatic cancer (i.e., the matrix metallo proteinase inhibitor [MMPI] or farnesyl transferase inhibitor [FTI] classes) with gemcitabine. The first of these was a study conducted by Bramhall et al.[36] in the United Kingdom comparing three doses of marimastat (an MMPI) against gemcitabine. A total of 414 patients were enrolled in this four-arm study, in which gemcitabine was administered at 1000 mg/m$^2$ in the 7-week first schedule against three other arms, of marimastat (10 mg, 20 mg, and 50 mg/day). Except in the high-dose arm, in which the 1-year survival was similar

**Table 1.** Single-agent studies of gemcitabine in advanced pancreatic cancer

| Study no. | Authors | Gemcitabine dose ($mg/m^2$) | *n* | PR (%)[a] | SD (%) | PR+SD (%) | CBR (%) | 1-Year sur. (%) | TTP (months) | MST (months) | Toxicity | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | Hematological (G3/4; %) | | | | |
| | | | | | | | | | | | Leuko | Neutro | Thromb | Anemia | Nonhematological |
| 1 | Casper[22] | 800 × q3 of 4 wk (max, 1500) | 44 | 11.0 | 31.8 | 42.8 | NA | 23.0 | 3.7 | 5.6 | Median WBC nadir, $3.8 \times 10^3/\mu l$ (1.6–9.3), Median ANC nadir, $2.0 \times 10^3/\mu l$ (0.4–7.2), Median platelet nadir, $123 \times 10^3/\mu l$ (30–245) | | | | Mild to moderate flu-like syndrome: all pts<br>Mild hemolytic-uremic syndrome: 1 pt |
| 2 | Carmichael[23] | 800 × q3 of 4 wk (max, 1000) | 34 | 6.3 | 18.8 | 25.1 | NA | NA | NA | 6.3 | 6.1 | 24.5 | 9.1 | 3.0 | G3 (nausea/vomiting 26.7%, diarrhea 3.3%, pain 3.3%, state of consciousness 3.3%),<br>G2 (cutaneous 10%, fever 20%, infection 6.7%, nausea/vomiting 20.0%, state of consciousness 13.3%) |
| 3 | Petrovic[28] | 1000 × 7 wk, then q3 of 4 wk | 11 | NA | NA | NA | 33.0 | 26.0 | NA | 6.65 | | | | | Well tolerated |
| 4 | Manzano[27] | 1000 × 7 wk, then q3 of 4 wk | 15 | NA | NA | NA | 26.6 | 39.0 | NA | NA | NA | 6.6 | NA | NA | G4 asthenia 6.6% |
| 5 | Kurtz[29] | 1000 × 7 wk, then q3 of 4 wk | 74 | 4.3 | 39.1 | 43.4 | 48.0 | NA | NA | 5.0 | NA | 27.0 | 14.0 | 22.0 | G3/4 (asthenia, 5 pts; nausea/vomiting, 4 pts; anorexia, 3 pts; partial occlusion-occlusion, 3 pts; edema, 1 pt; cardiac insufficiency, 1 pt; embolization of catheter, 1 pt; arterial hypotension, 1 pt; jaundice, 1 pt; dehydration, 1 pt; abdominal pain, 1 pt) |
| 6 | Aykan[26] | 1000 × 7 wk, then q3 of 4 wk | 14 | 14.3 | 50.0 | 64.3 | NA | 14.3 | NA | 6.0 | | | | | No G3/4 toxicity |
| 7 | Meyer[30] | 1000 × 7 wk, then q3 of 4 wk | 28 | 7.2 | 39.2 | 46.4 | NA | 14.3 | NA | 9.8 | 11 | NA | 18 | 8.0 | G3 (diarrhea, 7%; nausea, 7%; edema, 4%; alopecia, 20%) |
| 8 | Crino[24] | 1000 × 7 wk, then q3 of 4 wk | 33 | 12.1 | 45.5 | 57.6 | NA | NA | NA | 7.6 | 9 | NA | 12.0 | 12.0 (G2/3) | Nausea/vomiting G1/2 (24%/9%); G1/2 skin rash, 9%; peripheral edema 24%; asthenia, 39%; G1, alopecia 3% |
| 9 | Rothenberg[32] | 1000 × 7 wk, then q3 of 4 wk (max, 1250) | 74 | 10.5 | 29.8 | 40.3 | 27.0 | 4.0 | 2.53 | 3.85 | 9.8 | 26.2[b] | 4.9 | 11.4 | G4 (hemorrhage, 1.6%; vomiting, 1.6%),<br>G2/3 (constipation, 4.8%/1.6%; cutaneous, 9.5%/0%; fever, 14.3%/1.6%; hair loss, 1.6%/0%; infection, 0%/3.2%; nausea/vomiting, 28.6%/6.3%; oral mucositis, 1.6%/0%; pain, 3.2%/1.6%; peripheral neuropathy, 1.6%/0%; pulmonary, 1.6%/0%; state of consciousness, 1.6%/3.2%) |
| 10 | Okada[31] | (a) 1000 × q3 of 4 wk<br>(b) 1000 × 7 wk, then q3 of 4 wk | 11 | 18.2 | 36.4 | 54.6 | 28.6 | 18.2 | NA | 6.3 | 27.3 | 36.4 | 0.0 | 9.1 | G3/4 anorexia, 27.3%, G3 (nausea/vomiting, 9.1%; fatigue, 18.2%; GOT/GTP, 9.1%; weight loss, 9.1%) |

*n*, Number of patients; PR, partial response; SD, stable disease; CBR, clinical benefit response; TTP, time to progression; MST, median survival time; *G*, toxicity grade; leuko, leukopenia; neutro, neutropenia; thromb, thrombocytopenia; WBC, white blood cell; ANC, absolute neutrophil count; NA, not available; wk, week; pt, patient; sur., survival

[a] Calculated including complete response

[b] Granulocytopenia

**Table 2.** Randomized studies of gemcitabine in Advanced pancreatic cancer

| Study no. | Authors | Drug | Dose (mg/m²) | *n* | PR (%)[a] | SD (%) | PR+SD (%) | CBR (%) | 1 Year sur (%) | PFS (months) | MST (months) | Toxicity | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | Hematological (G3/4): % | | | | |
| | | | | | | | | | | | | Leuko | Neutro | Thromb | Anemia | Nonhematological |
| 1 | Burris[35] | Gem | 1000 × 7 wk, then q3 of 4 wk (max, 1250) | 63 | 5.4 | 39.0 | 44.4 | 23.8 | 18.0 | NA | 5.65 TTP (2.1) | 9.7 | 25.9 | 9.7 | 9.7 | G3/4 (nausea/vomiting 12.7%), G3 (diarrhea, 1.6%; constipation, 3.2%; state of consciousness, 1.6%; pain, 1.6%) |
| | | 5FU | 600 weekly | 63 | 0.0 | 19.0 | 19.0 | 4.8 | 2.0 | NA | 4.41 TTP (0.9) | 1.6 | 4.9 | 1.6 | 0.0 | G3 (nausea/vomiting, 4.8%; diarrhea, 4.8%; constipation, 1.6%; state of consciousness, 1.6%) |
| 2 | Bramhall[36] | Gem | 1000 × 7 wk, then q3 of 4 wk | 103 | 26.0 | NA | NA | NA | 19.0 | 3.8 | 5.5 | 2.0 | 7.0[b] | 5.0 | 2.0 | G3/4 (cardiac function, 1%; constipation, 1%; fever in absence of infection, 1%; infection, 2%; local, 1%; nausea, 4%; neurocortical [cortical], 5%; [motor], 4%; pulmonary, 9%; skin, 3%) |
| | | Marimastat | 5 mg b.i.d. | 104 | 2.8 | NA | NA | NA | 14.0 | 1.8 | 3.6 | 0.0 | 1.0[b] | 3.0 | 4.0 | G3/4 (cardiac dysrhythmias, 1%; diarrhea, 1%; musculoskeletal, 7%; nausea, 2%; neurocortical[cerebellar], 2%; [vision], 1%; pulmonary, 3%; weight gain or loss, 1%) |
| | | | 10 mg b.i.d. | 105 | 2.8 | NA | NA | NA | 14.0 | 1.9 | 3.5 | 0.0 | 0.0[b] | 0.0 | 3.0 | G3/4 (musculoskeletal, 7%; nausea, 1%; neurocortical[motor], 1%; vomiting, 1%) |
| | | | 25 mg b.i.d. | 102 | 2.8 | NA | NA | NA | 20.0 | 1.9 | 4.1 | 0.0 | 0.0[b] | 2.0 | 2.0 | G3/4 (musculoskeletal, 12%; nausea, 1%; neurocortical[motor], 1%; pulmonary, 1%) |
| 3 | Moore[37] | Gem | 1000 × 7 wk, then q3 of 4 wk | 139 | 4.3 | 44.6 | 48.9 | NA | 25.0 | 3.4 | 6.7 | NA | 34.5 | 6.5 | 10.1 | G3/4 (nausea, 3.6%; vomiting, 5.0%; lethargy, 5.8%) |
| | | Bay-12-9566 | 800 mg p.o. b.i.d. | 138 | 0.7 | 22.5 | 23.2 | NA | 10.0 | 1.7 | 3.7 | NA | 2.2 | 0.0 | 10.1 | G3/4 (Nausea, 8.0%; vomiting, 2.9%; lethargy, 6.5%) |
| 4 | Lersch[38] | Gem | 1000 × 7 wk, then q3 of 4 wk | 30 | 3.3 | 36.7 | 40.0 | NA | NA | NA | 4.4 | NA | 17.0 | 17.0 | NA | Nausea/vomiting, diarrhea were reported equally with both drugs, but were more severe with gem |
| | | SCH66336 | 200 mg p.o. b.i.d. | 33 | 6.1 | 18.2 | 24.3 | NA | NA | NA | 3.3 | NA | 3.0 | 0.0 | NA | |
| 5 | Colucci[41] | Gem | 1000 × 7 wk then q3 of 4 wk | 51 | 10 | NA | NA | 45 | NA | NA | NA | 3.0 | 13.0 | 3.0 | 3.0 | G3/4 nausea/vomiting, 3% |
| | | Gem + CDDP | 1000 × 7 wk, then q3 of 4 wk. 25 D1 | 52 | 31 | NA | NA | 38 | NA | NA | NA | 6.0 | 26.0 | 3.0 | 10.0 | G3/4 (nausea/vomiting, 23%; diarrhea, 3%) |
| 6 | Di Costanzo[39] | Gem | 1000 × 7 wk, then q3 of 4 wk | 49 | 8.3 | 29.2 | 37.5 | NA | NA | 3.2 | 7.2 | 2.0 | NA | 0.0 | 6.0 | G3 (asthenia, 2%; fever, 2%) |
| | | Gem + 5FU | 1000 × 7 wk, then q3 of 4 wk. 200 × 6 wk, CI, then q3 of 4 wk | 45 | 11.6 | 27.9 | 39.5 | NA | NA | 4.2 | 6.9 | 2.0 | NA | 2.0 | 7.0 | G3 (mucositis, 5%; nausea/vomiting, 2%; asthenia, 2%; fever, 5%) |
| 7 | Berlin[40] | Gem | 1000 × q3 of 4 wk | 163 | NA | NA | NA | NA | NA | NA | 5.4 | 16.0 | 5.0[c] | NA | NA | G3/4 diarrhea, 4% |
| | | Gem + 5FU | 1000 × q3 of 4 wk 600 × q3 of 4 wk | 164 | NA | NA | NA | NA | NA | NA | 6.7 | 29.0 | 7.0[c] | NA | NA | G3/4 diarrhea, 10% |
| 8 | Heinemann[42] | Gem | 1000 × q3 of 4 wk | 54 | NA | NA | NA | NA | NA | NA | NA | 5.5 | NA | 7.4 | 9.2 | G3/4 (mucositis, 3.7%; diarrhea, 7.4%), G3 nausea/vomiting, 3.7% |
| | | Gem + CDDP | 1000 × q3 of 4 wk. 50 (d1,15) q4 w | 46 | NA | NA | NA | NA | NA | NA | NA | 13.0 | NA | 8.6 | 13.0 | G3/4 (mucositis, 4.3%; diarrhea, 10.8%), G3 nausea/vomiting, 33% |

Gem, Gemcitabine; Max, maximum; *n*, number of patients; PR, partial response; SD, stable disease; CBR, clinical benefit response; PFS, progression-free survival; MST, median survival time; TTP, time to progression; G, toxicity grade; leuko, leukopenia; neutro, neutropenia; thromb, thrombocytopenia; 5FU, 5 fluorouracil; CDDP, cisplatin; CI, continuous IV infusion

[a] Calculated including complete response

[b] Granulocytes/bands

[c] Granulocytopenia

to that with gemcitabine, all other efficacy variables (median survival, progression-free survival, improvement of performance status, and pain) were all better for the patients who underwent gemcitabine treatment than for those treated with any doses of marimastat. Table 2 depicts the details of these data.

Another study was also conducted to compare gemcitabine versus yet another MMPI (Bay 12-9566).[37] This study, led by Moore et al.,[37] was conducted by the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) at 41 sites throughout North America. However, this study was terminated early because the results were too unfavorable for this new agent, which made further enrollment unethical for the patients. Overall, among the 277 patients enrolled (out of the original plan for 350 patients), gemcitabine was superior to Bay 12-9566 in terms of overall survival (6.7 vs 3.7 months), progression-free survival (3.4 vs 1.7 months), and objective responses (partial response [PR] + stable disease [SD]; 48.9% vs 23.2%). Side effects were manageable for both treatments.

Another randomized study was published recently using an FTI (SCH 66336) against gemcitabine.[38] The study, led by Lersch et al.,[38] enrolled 63 patients in two arms (30 patients for gemcitabine and 33 for SCH 66336). The primary endpoint was 3-month progression-free survival, which was 31% for the gemcitabine-treated patients and 23% for the SCH 66336 patients. Response rate (see Table 2) and median survival time were also higher for the gemcitabine arm. Besides these studies, four other randomized studies have compared gemcitabine alone versus gemcitabine combinations (i.e., with 5-FU or cisplatin).[39–42] They are discussed below, under the heading "Gemcitabine in combination with other cytotoxic drugs".

## Treatment investigational new drug program

A large-scale Treatment Investigational New Drug Program (TIND) for gemcitabine was conducted in 1995–1996 in 3023 patients with locally advanced or metastatic pancreatic cancer.[43] Gemcitabine was administered using the 7-week initial regimen. There were 1.4% complete responses (CRs) and 10.6% partial responses (PRs), with an overall response rate of 12% noted. The median overall survival was 4.8 months, and 1-year survival was 15%. A parameter similar to CBR, called disease-related symptom improvement (DRSI) was used in this study. DRSI was defined as improvement in either pain, or analgesic class, or a 20 point increase in the Karnofsky performance scale; or, if all three were stable, a 7% increase in dry weight compared with baseline. Cumulative DRSI responses were observed in 13.5%, 16.6%, 18.0%, and 18.4% after the first, second, third, and fourth treatment cycles of gemcitabine, respectively. The most commonly reported toxicities were fever (7.3%), pain (6.8%), asthenia (6.0%), and abdominal pain (5.5%), with only 4.6% of patients needing to discontinue therapy because of adverse events. Overall, this large scale, open-enrollment study confirmed the safety and efficacy profiles of gemcitabine observed in earlier studies.

## Other administration modalities for gemcitabine

### *Fixed dose-rate infusion regimen (10 mg/min per m$^2$)*

Because of its unique metabolic mechanism, it was found that if gemcitabine was administered at an infusion rate of 10 mg/m$^2$ per min instead of the conventional 30-min infusion schedule, the level of its active metabolite, gemcitabine triphosphate (dFdCTP) would be increased, and thus might result in a potential increase in cell killing.[44] A phase II trial was conducted by Tempero et al.[45] to test this hypothesis. Patients were randomized to receive either gemcitabine 2200 mg/m$^2$ as a 30-min infusion or gemcitabine 1500 mg/m$^2$ at 10 mg/m$^2$ per min. The dosing schedule for both regimens was the same, at every 3 out of 4 weeks. In the 67 patients that were enrolled, the overall response rate was 16.6% in the fixed dose-rate arm compared with 2.7% in the standard infusion arm. In addition, both the median survival (6.1 vs 4.7 months) and 1-year survival (23% vs 0%) were in favor of the fixed dose-rate infusion regimen. However, hematological toxicities observed in the patients treated with this fixed dose-rate infusion were about twice as high as those in the other arm (with approximately triple the level of the active metabolite, dFdCTP, detected), although this was still manageable, with no major sequela noted. Overall, further studies will be helpful to better define the role of this infusion schedule for other patients in the future.

### *High-dose infusion*

While most studies used the customary 1000–1250 mg/m$^2$ dose, a higher dose of gemcitabine might be feasible. A phase I study was performed by Fossella et al.[46] in patients with non-small cell lung cancer, using a dosing range of 1000–2800 mg/m$^2$. The maximum tolerated dose was found to be 2200 mg/m$^2$ per week for a 3 out of 4-week schedule. Ulrich-Pur et al.[47] subsequently conducted a phase II study in pancreatic cancer patients, using 2200 mg/m$^2$ every other week. Among the 43 patients treated, there was 1 CR and there were 8 PRs, with an overall response rate of 20.9%. In addition, 18 other patients (41.9%) had SD. The median survival was 8.8 months, and 1-year survival was 26.3%; 44% of

the patients also had CBR, with a median duration of response of 27 weeks. Toxicities were modest, with grade 3 leukopenia (12%), neutropenia (23%), anemia (2%), and alopecia (5%) being the most commonly noted. Overall, this study suggested that this alternate-week high-dose regimen was feasible for pancreatic cancer patients.

*Intraarterial infusion of gemcitabine*

Intraarterial administration has provided yet another alternative for the treatment of pancreatic cancers, especially in earlier-stage diseases in which the tumor burden was mainly locoregional in nature. Two pilot studies were conducted to test such use.[48,49] In the study of Spagnuolo et al.,[48] gemcitabine was administered at a dose of 1500 mg/m$^2$ through superselective arterial or celiac axis infusion every 28 days. The median number of cycles of treatment was 2 (range, 1–3). Ten patients were treated, and PRs were noted in 2 patients, with 4 additional patients achieving minor responses. The authors reported no significant adverse events for this regimen. The second study was by Weissmann and Ludwig,[49] in which gemcitabine, at 1200 mg/m$^2$, was intraarterially administered to the celiac artery every 28 days. The median number of cycles of therapy was 2 (range, 1–6). Among the 15 pancreatic cancer patients, 2 achieved CRs, with an additional 4 patients achieving minor responses. The regimen was well tolerated, with hematologic toxicities noted in 4 patients. Future studies will be helpful in further define this mode of treatment in view of these early encouraging data.

*Gemcitabine in combination with other cytotoxic drugs*

The mild toxicity profile of gemcitabine, along with its therapeutic efficacy and lack of cross-resistance with 5-FU, makes it an attractive partner as combination therapy with other oncolytic agents. Quite a few studies have been published, and below is a review of those with the greatest interest.

*Gemcitabine and 5-FU.* Many phase II studies have evaluated gemcitabine with 5-FU in different settings (e.g., bolus, continuous IV infusion, high dose, and with/without folinic acid).[18,50–54] Results have been somewhat variable, although a number of the studies showed some increase in response rate, CBR, and/or survival. However, two randomized studies recently published showed a somewhat different picture. The study by Di Costanzo et al.[39] in Italy showed that the outcomes of the 43 patients who underwent standard schedule gemcitabine with 5-FU (as continuous IV infusion) were not significantly better than those of the 48 other patients treated with gemcitabine alone. Overall, both response rate and survival were not remarkably different between the two arms (see Table 2).

Another larger-scale randomized phase III study (Eastern Cooperative Oncology Group [ECOG] 2297), led by Berlin et al.,[40] also showed similar findings. In this study of 327 patients, patients were randomized to receive either gemcitabine monotherapy at the standard schedule ($n = 163$) or gemcitabine plus 600 mg/m$^2$ of 5-FU ($n = 164$) as IV bolus weekly in a 3 out of 4 weeks cycle. Overall survival, the primary study objective, was 6.7 months for the combination arm and 5.4 months for the monotherapy, but the results were statistically insignificant ($P = 0.11$). In addition, there was slightly more leukopenia and diarrhea reported for the combination than for the gemcitabine monotherapy. Thus, despite the early optimism for the gemcitabine/5-FU combination, unless other large-scale randomized studies, using perhaps a different dose or dosing schedule of 5-FU, are able to demonstrate otherwise, there is currently no clinical evidence to suggest that combination gemcitabine therapy with 5-FU is better than gemcitabine alone.

*Gemcitabine and cisplatin.* The clinical efficacy of gemcitabine and cisplatin for several solid tumors (e.g., nonsmall cell lung cancer [NSCLC], bladder, breast, ovarian, etc), along with the synergism demonstrated in preclinical evaluations has led to the investigation of this combination in patients with pancreatic cancer.[55–59] Two nonrandomized phase II studies have been published in which the survival and responses seemed to be in favor of the combination, in terms of objective response and/or CBR observed.[60,61] On the other hand, in a randomized study, by Colucci et al.,[41] in which gemcitabine plus cisplatin were compared against gemcitabine alone, the outcomes were mixed. Among the 62 assessable patients from the 103 patients enrolled, the combination provided a much higher objective response (31% vs 10%), but more patients achieved CBR in the gemcitabine alone arm (45% vs 38%; see Table 2). Toxicities observed were also higher in the combination arm, although they were manageable. Additional analyses for the entire 103 patients enrolled were pending. Another randomized study, by Heinemann et al.,[42] using a different dose and schedule for the gemcitabine-cisplatin combination was also ongoing. Early data release showed a slightly better tolerated safety profile than other Gem/Cis studies data, although efficacy data were not yet available. Details of these two randomized studies are depicted in Table 2. Overall, until the final data become available, it is probably a little premature to speculate on the role of this combination.

*Gemcitabine and other oncolytic agents*

Many other gemcitabine combination studies have been published.[62–79] For example, studies with combinations with taxotere, oxaliplatin, epirubicin, mitomycin C, octreotide, tamoxifen, marimastat, capecitabine, and irinotecan, as well as multidrug regimens (epirubicin, cisplatin, and 5-FU), have been conducted. Some of these studies have had encouraging results. However, because the majority of these studies had small sample sizes and were nonrandomized in nature, until the time when larger randomized phase III data become available, these results could only be viewed as encouraging early data at present.

*Gemcitabine and radiation therapy*

Gemcitabine is known as a potent radiosensitizer from preclinical studies, and there is much interest in investigating its use with radiation in pancreatic cancer.[80–82] Such use has often involved expansion beyond the customary focus of treatment of advanced pancreatic cancer to earlier-stage diseases. Quite a few studies have been published, and the objectives varied from palliative to curative or neoadjuvant or adjuvant use.[83–102] Besides the different intentions, the dosing strategies also varied, from simultaneous administration to sequential delivery. However, data of most of these studies were not fully available as they were published mainly in the abstract format. Table 3 depicts the details of these studies.

As can be seen from the data presented, in Talbe 3, a wide variety of regimens was tested. Nonetheless, it seemed obvious that, because of the radiosensitization effect involved, when gemcitabine was given simultaneously with radiation, the dose of one of the two would likely need to be reduced. Because the majority of these studies were dose-finding in nature, only some of the studies had efficacy reported, and these early data seemed encouraging. Overall, among this wide variety of regimens, the response rates varied from 16.7% to 57.1%, and 1-year survival was 60%–70%, with downstaging of as much as 70% noted in some cases.

With a reduced dose, toxicities were generally more manageable, with leukopenia, thrombocytopenia, fatigue, anorexia, nausea/vomiting, diarrhea, and dehydration the most commonly noted. Also, there were suggestions from some studies that toxicities might be reduced with the shrinking field technique, and/or with three-dimensional planning, as toxicities were generally dependent on the radiation volume. However, a word of caution seems necessary; despite these encouraging data, the optimal regimen(s), in terms of dose, schedule, and sequence, have not been completely clarified at present. Thus, chemoradiation therapy with gemcitabine should only be considered as experimental in nature and patients should not be treated outside a controlled clinical trial setting.

*Adjuvant use*

While there have been scattered anedoctal successes with the use of adjuvant gemcitabine after pancreatic cancer surgery, there has been no randomized study completed thus far to establish such use. An animal study published recently showed that nude mice implanted with BxPC-3 pancreatic cancer cells achieved a much lower rate of local recurrence if adjuvant gemcitabine was added after surgery compared with results without it (28.6% vs 70.6%).[103] In addition, distant metastases were also found to be 58% lower in the surgery + gemcitabine group than in the group with surgery alone.

Only a handful of small pilot studies have been published so far on the adjuvant use of gemcitabine. The first was a phase II study by van Laethem et al.[102] in Belgium. Seventeen patients with stage II and III pancreatic cancers underwent surgical resection, and within 8 weeks after the operation, they received gemcitabine 1000 mg/m$^2$ on days 1 and 8 every 21 days for three cycles, followed by the simultaneous use of gemcitabine 300 mg/m$^2$ per week with 40 Gy of radiation, delivered over 6 weeks. Results showed that the 1-year survival was 70%, overall survival was 12 months, and disease-free survival was 8 months. Toxicities were moderate, with 3 of the 17 patients having experienced grade 3–4 hematological toxicities and 4 patients with nausea and vomiting.

Another study, by Kachnic et al.,[101] investigated the adjuvant use of gemcitabine, at 40 mg/m$^2$ per week, along with 50.4 Gy of radiation, for patients after pancreatic cancer resection. Subjects without disease progression after the initial chemoradiation were given two additional cycles of gemcitabine at 1000 mg/m$^2$, administered in a 4-week schedule. Fifteen patients had been enrolled, and 9 completed the whole treatment. Concurrent gemcitabine and radiation were administered successfully in 80% of the patients without treatment delays. Responses were too early to assess, but 12 patients were alive without disease progression at a median follow-up of 5 months. Toxicities were modest, with only grade 3 anemia/thrombocytopenia (3 patients), fatigue (3 patients), and nausea (1 patient) noted.

Two small studies also investigated the use of a sequential adjuvant regimen with initial 5-FU plus radiation followed by gemcitabine.[104,105] The data from these studies were early, but both suggested the feasibility of such an approach. On the other hand, a large-scale randomized phase III study comparing gemcitabine at a

**Table 3.** Studies of gemcitabine with radiation in pancreatic cancer

| Study no. | Authors | RT dose (Gy) | Gemcitabine dose ($mg/m^2$) | *n* | PR (%)[a] | SD (%) | PR +SD (%) | 1 Year sur (%) | MST (months) | Toxicity |
|---|---|---|---|---|---|---|---|---|---|---|
| Definitive therapy | | | | | | | | | | |
| 1 | McGinn[83] | 50.4 | 200, 300, 400, 500 1/wk | 13 | NA | NA | NA | NA | NA | 300 $mg/m^2$, DLT, 1 pt G3 neutro<br>400 $mg/m^2$, no DLT<br>500 $mg/m^2$, ongoing |
| 2 | Wolff[84] | 30 | 400, 500 × 7 wk<br>(48–72 h before RT) | 12 | 30 | NA | NA | NA | NA | 400 $mg/m^2$, hospitalization (4/9)<br>500 $mg/m^2$, hospitalization for nausea, vomiting and dehydration (3/3)<br>350 $mg/m^2$, ongoing |
| 3 | Abad[85] | cycle 1: 45<br>cycle 2: —<br>cycle 3: 22.5 | cycle 1: 200 − 600 × 6 wk<br>cycle 2: 1000 × 3 wk<br>cycle 3:— | 6 | 16.7 | 33.3 | 50 | NA | NA | 200 $mg/m^2$, G4 diarrhea (1/3)<br>G1/2 nausea/vomiting (4 pts), G1 diarrhea (1 pt)<br>2 pts, too early for evaluation of efficacy<br>MTD, 200 $mg/m^2$ |
| 4 | Brierley[86] | 25, 30, 35, 40 | 40 × 2/wk | 14 | NA | NA | NA | NA | NA | 25 Gy, no G3/4 tox<br>30 Gy, G3 thromb/neutro, 1 pt; G4 diarrhea/G3 fatigue, 1 pt<br>35 Gy, no G3/4 tox<br>40 Gy, ongoing |
| 5 | Wong[87] | A: 25–40 (split)<br>B: 35–52.5 (continuous) | 40 × 2/wk | 23<br>19 | NA | NA | NA | NA | NA | 25 Gy (split), no DLT<br>30 Gy (split), DLT 1 pt (G4 diarrhea/fatigue)<br>35, 40 Gy (split), no DLT<br>35 Gy (continuous 4 wk), DLT 1/6 (G3 diarrhea/fatigue)<br>43, 47 Gy (continuous 5 wk), DLT 2/12 G3 (nausea/fatigue, dehydration)<br>52.5 Gy, ongoing |
| 6 | Herscher[88] | 54–55.8 | 350, 440, 550 × 1/wk × 5 | 19 | NA | NA | NA | NA | NA | DLT, neutro, thromb; MTD, 440 $mg/m^2$ |
| 7 | Epelbaum[89] | 50.4 | Gem (alone) 1000 × 7 wk<br>400 × 3 wk q4 w × 2<br>Gem (alone) 1000 × 3 wk q4 w | 20 | 20 | 30 | 50 | NA | 12 | G3/4 (nausea/vomiting, diarrhea, 5 pts; neutropenic fever, 2 pts) in case of chemo RT severe abdominal wall pain (few months after completion of RT), 3 pts; pancreatectomy (2 pts), histological no active tumor (1 pt), complete surgical resection (1 pt); CBR after induction phase, 50% |
| 8 | Blackstock[90] | 50.4 | 40 2/w × 5.5 wk<br>Gem (alone) 1000 × 3 wk q4 w × 5 | 43 | NA | NA | NA | NA | 7.9 | G3/4 hemato tox, 42%/18%; G3/4 gastrointenstinal tox, 34%/8% |
| 9 | Mustacchi[91] | 45–55.8 | Gem (alone) 1000 × 3 wk q4 w × 2<br>500 × 6 wk<br>Gem (alone) 1000 × 3 wk q4 w × 2 | 15 | 35.7 | 35.7 | 71.4 | 60 | 17.3 | G3 abdominal pain (9/15), G2/3 asthenia (13/15), anorexia (13/15), G2 diarrhea (2/15), G1/2 [nausea (3/15), abdominal discomfort (4/15), thromb (1/15)] |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Palliative therapy | | | | | | | | | | |
| 10 | Maurer[92] | 50.4 | 200, 250, 300, 350 (1 h before RT) day 1, 8, 15, 22, 29 | 16 | NA | NA | NA | NA | NA | 200 mg/m²/250 mg/m², no G3/4<br>300 mg/m², G3 leuko (2/6), G1/2 nausea/vomiting, 1 pt; G4 AST/ALT, 1 pt |
| 11 | Reyes-Vidal[93] | 45 | 200, 225, 300, 325 × 5 wk (4–8 h before RT) | 14 | 57.1 | 42.9 | 100.0 | NA | NA | Nausea/vomiting (12/14, G1/2 7 pts/5 pts)<br>G4 diarrhea, 1 pt<br>G3 (neutro, 3 pts; anemia, 1 pt; diarrhea, 1 pt; respiratory, 1 pt; hepatitis, 1 pt) |
| 12 | McGinn[94] | 24–42 | 1000 × 3 wk q4 w followed by gem (alone) 1000 × 3 wk × 1 | 37 | 30 | NA | NA | NA | 11.6 | 30 Gy, 1 pt DLT, G4 vomiting<br>42 Gy, 2 pts (DLT G4 vomiting, ulceration [gastric/duodenal])<br>(no investigation of higher dose because of DLT[2/6], the potential for late tox) |
| 13 | Antonisse[95] | 24 | 300 × 3 wk q4 w followed by gem (alone) 1000 weekly | 21 | NA | NA | NA | NA | 16.2 | Mild nausea/vomiting, 17 pts; mild abdominal pain, 7 pts;<br>CA19-9 reduction, 82% (14/17); palliation of pain, 72% (13/18); pain medication reduced, 73% (11/15) |
| Neoadjuvant therapy | | | | | | | | | | |
| 14 | Blackstock[96] | 50.4 | 20, 40, 60 × 2/wk | 19 | 20 | NA | NA | NA | 12.3 | |
| | | | | | | | | | | Diarrhea / Neutro / Thromb / Nausea/vomiting<br>*n* G3 G4 G3 G4 G3 G4 G3 G4<br>20 mg/m² 6 1 0 0 0 0 0 1 0<br>40 mg/m² 6 0 0 1 0 1 0 1 0<br>60 mg/m² 6 0 0 3 0 3 0 1 0<br>40 mg/m²twice-weekly was well tolerated |
| 15 | Wolff[97] | 30 | 400 × 7 wk | 18 | NA | NA | NA | NA | NA | 9 pts completed treatment<br>G3 neutro, 44%; G3 thromb, 11%; 6 pts successful pancreaticoduodenectomy, histological complete response (2/6) |
| 16 | Hoffman[98] | 50.4 | 300, 400, 500, 600 × 6 wk followed by gem (alone) 1000 × 3 wk q4 w × 4 | 18 | NA | NA | NA | NA | NA | 400 mg/m²: G4 (GI hemo, 1 pt; nausea/vomiting, 1 pt), G3 nausea, 1 pt<br>500 mg/m²: G4 (neutro, 1 pt; anorexia, 1 pt), G3 anorexia, 1 pt<br>600 mg/m²: G4 dehydration, G3 (thromb, 1 pt; pulmonary embolus, 1 pt)<br>12 pts (71%) had resection |
| 17 | Lange[99] | 24 | 300 × 3 wk q4 w followed by gem alone × 3 wk q4 w | 22 | 31.8 | 45.0 | 76.8 | NA | 9 | G3/4 (neutro, 4.5%; thromb, 13%); G1/2 (nausea/vomiting, 86%; diarrhea, 45%), ulceration[gastric/duodenal], 31.8% (bleeding 18%) |
| 18 | Hietaniemi[100] | 50.4 | 20, 50, 100 × 2/wk | 16 | 45.5 | 27.3 | 72.8 | NA | NA | 100 mg/m², DLT (G4 fatigue, 2 pts; G4 nausea, 1 pt; G3 thromb, 1 pt; G3 diarrhea, 1 pt; infection, 1 pt)<br>MTD, 50 mg/m²; 10/16 (62.5%) received surgery (radical, 8 pts; palliative, 2 pts) |
| Adjuvant therapy | | | | | | | | | | |
| 19 | van Laethem[102] | 40 | Gem (alone) 1000 × 2 wk q3 w × 3<br>300 weekly | 17 | NA | NA | NA | 70 | 12 | G3/4 hemato, 17% (3/17); G3/4 nausea/vomiting, 23% (4/17) |
| 20 | Kachnic[101] | 50.4 | 40 × 2/wk followed by gem (alone) 1000 × 3 wk q4 w × 2 | 15 | NA | NA | NA | NA | NA | G3 (anemia/thromb, 3 pts; fatigue, 3 pts; nausea, 1 pt)<br>No radiation recall |

RT, Radiation therapy; *n*, number of patients; PR, partial response; SD, stable disease; MST, median survival time; G, toxicity grade; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; CBR, clinical benefit response; leuko, leukopenia; neutro, neutropenia; thromb, thrombocytopenia; CA-19-9, carbohydrate antigen 19-9

[a] Calculated including complete response

standard dose for six cycles versus observation alone after pancreatic cancer surgery might provide a better answer in the future.[106] This study, led by Oettle et al.,[106] is now underway in Germany. The study planned to enroll 368 patients, and the published data for the first 113 patients enrolled so far have revealed no major toxicities. Efficacy data are pending at the present time.

*Neoadjuvant use*

Very few data are available on the neoadjuvant use of gemcitabine, and all such studies were with radiation. Sasson et al.[107] conducted a retrospective review of 107 patients who underwent curative surgery for pancreatic cancer (90 Whipples, 11 total, and 6 distal pancreatectomies). Of these patients, 49 had surgery alone and 58 received neoadjuvant chemoradiation (25 with gemcitabine and 33 with 5-FU-mitomycin C) prior to the operation. It was found that neoadjuvant therapy resulted in greater fibrosis (74%) in the tumor compared with findings in patients without this therapy (39%), which in turn was correlated with positive survival outcomes. The median survival for the neoadjuvant groups was higher than that for those without it (21 vs 16 months). Although this study did not distinguish individual differences in the outcomes between the gemcitabine and 5-FU-mitomycin C groups, the findings were suggestive of gemcitabine being feasible for neoadjuvant use.

Another neoadjuvant study, conducted by Hietaniemi et al.,[100] also showed encouraging results. In that study, a total of 50.4 Gy radiation (in 180-cGy fractions) was delivered, along with an escalating dose of gemcitabine, at 20, 50, and 100 mg/m$^2$ administered twice weekly. Of the 11 evaluable patients among the 16 enrolled, there were 1 with CR, 4 with PRs, 3 with SD, and 3 with progressive disease, with an overall response rate of 45.5%. Except for 2 patients who had distant metastasis, 10 patients proceeded with surgery (8 radical and 2 palliative) after the neoadjuvant treatment, and surgeries for the other 4 patients were pending. Dose-limiting toxicities were grade 4 fatigue (2 patients), nausea (1 patient), and grade 3 thrombocytopenia-diarrhea-infection (1 patient). Most toxicities occurred at the 100 mg/m$^2$ dose, and the maximum tolerated dose of gemcitabine was therefore identified at 50 mg/m$^2$. Results of other similar studies for neoadjuvant use can be found in Table 3. Overall, despite these interesting data, a large-scale randomized study will be needed in the future to further clarify the role of gemcitabine in this setting.

## Treatment cycles versus objective responses and survival

There has been a lot of controversy in regard to the optimal number of cycles of treatment for patients to accomplish the best therapeutic outcomes. The number of treatment cycles would obviously depend on the patients' tolerance to the therapy, which, in turn, would be related to factors such as performance status, underlying medical conditions, disease stage, etc. In addition, with a higher dose or a longer exposure, the potential increase in cancer kill might be negated by the corresponding increase in toxicities for most cytotoxic agents. However, gemcitabine is known to be an agent with a relatively mild toxicity profile. In fact, results from the Ulrich-Pur study (high-dose infusion)[47] and the Tempero study (fixed dose rate infusion with higher active metabolites)[45] were both suggestive that increased responses and survival could be achieved with manageable toxicities. In the Treatment IND program reported by Storniolo et al.,[43] cumulative DRSI responses were noted to be increased from 13.5% after the first cycle to 18.4% at the fourth cycle of gemcitabine treatment. In the study by Heinemann et al.,[108] remission of the tumor was not noted until a median of five cycles of chemotherapy had been delivered.

In this review of the presented studies, there are some suggestions that perhaps the number of cycles of therapy (depicted as the number of treatment courses delivered) might have some positive correlation with the observed responses and survival. Figure 1 depicts a plot of this relationship. Unfortunately, there were only very few studies in which these data were available to be included in the figure. Nevertheless, there seems to be a tendency towards a finding that perhaps a sufficient number of cycles might be needed for the benefits of gemcitabine therapy to be fully appreciated. Thus, patience in administering a sufficient amount of treatment may pay off in some cases.

## Summary and conclusions

From the data of the various clinical trials reviewed in this report, gemcitabine has been shown to benefit patients with advanced pancreatic cancer in multiple areas. Figure 2 illustrates the overall results of gemcitabine treatment in ten single-agent studies, along with the data from the gemcitabine arm of eight randomized studies. Overall, these data show that gemcitabine has consistently benefited these patients, in terms of objective responses, especially in terms of disease stabilization, survival, and clinical benefit responses, such as pain alleviation and improved performance status. Gemcitabine has also demonstrated, in randomized tri-

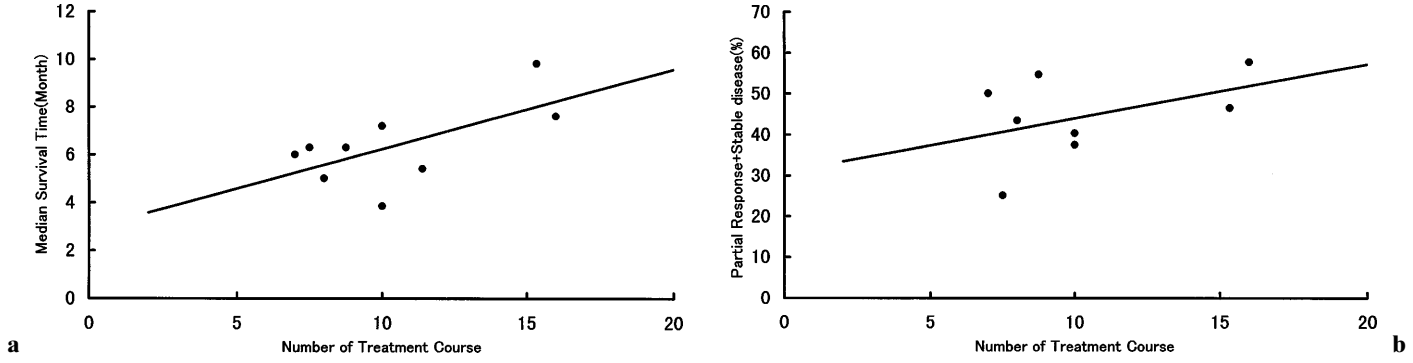


**Fig. 1.** **a** Median survival time versus number of treatment courses of gemcitabine therapy. **b** Objective reseponses versus number of treatment courses of gemcitabine therapy. **a** y = 0.332060x + 2.915521; $r = 0.63644$ ($P = 0.0653$). **b** y = 1.309950x + 30.838905; $r = 0.43922$ ($P = 0.2762$)

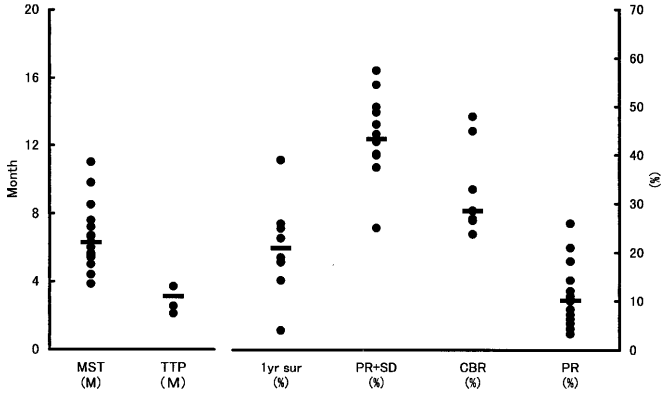


**Fig. 2.** Overall summary of median and ranges of various efficacy parameters for all studies of gemcitabine as single therapy (plus data from the gemcitabine arm of eight randomized studies) in advanced pancreatic cancer. *MST*, Median survival time; *TTP*, time to progression; *PR*, partial response; *SD*, stable disease; CBR, Clinical benefit response; *sur*, survival; *M*, months

als, superiority over 5-FU, MMPIs, and FTI, as well as efficacy in patients that failed prior 5-FU therapy. Overall, with its proven efficacy and favorable safety profile, gemcitabine has been widely accepted as the standard of care for patients with advanced pancreatic cancer worldwide.

Numerous clinical studies also show the combinability of gemcitabine with other oncolytic agents in combination use, although the optimal agent or dosing regimen has not yet been established. Different modalities of administration, such as fixed dose-rate infusion of 10 mg/m$^2$ per min, high-dose infusion, or intraarterial use, have also been tested, with encouraging results. Combination with radiation, as well as exploration of neoadjuvant or adjuvant uses, have been attempted, but data from many of these ongoing studies are pending at present. In summary, gemcitabine represents a major step forward in the chemotherapy of advanced pancreatic cancer and this agent has undoubtedly established its role as the standard of care in the management of these patients. With further understanding of the genetics and disease mechanism of pancreatic cancer, it is anticipated that future studies will test combinations of gemcitabine with other target biological agents.[109,110] Thus, in the future, new optimism for the better management of patients with this dismal disease, using novel therapies along with gemcitabine, will not be an unreasonable expectation.

## References

1. Tominaga S, Kuroishi T (1998) Epidemiology of pancreatic cancer. Semin Surg Oncol 15:3–7
2. Landis SH, Murray T, Bolden S, Wingo PA (1999) Cancer statistics. CA Cancer J Clin 49:8–31
3. Anonymous (1999) American gastroenterological association medical position statement: epidemiology, diagnosis, and treatment of pancreatic ductal adenocarcinoma. Gastroenterology 117:1463–1484
4. Barkin JS, Goldstein JA (2000) Diagnostic and therapeutic approach to pancreatic cancer. Biomed Pharmacother 54:400–409
5. Hawes RH, Xiong Q, Waxman I, Chang KJ, Evans DB, Abbruzzese JL (2000) A multispecialty approach to the diagnosis and management of pancreatic cancer. Am J Gastroenterol 95:17–31
6. Wanebo HJ, Vezeridis MP (1996) Pancreatic carcinoma in perspective: a continuing challenge. Cancer 78:580–591.
7. Sohn TA, Yeo CJ (2001) The molecular genetics of pancreatic ductal carcinoma: a review. Surg Oncol 9:95–101
8. Blaszkowsky L (1998) Treatment of advanced and metastatic pancreatic cancer. Front Biosci 3:214–225
9. Glimelius B (1998) Chemotherapy in the treatment of cancer of the pancreas. J Hepatobiliary Pancreat Surg 5:235–241
10. Sporn JR (1999) Practical recommendations for the management of adenocarcinoma of the pancreas. Drugs 57:69–79
11. Van Riel JM, Van Groeningen CJ, Pinedo HM, Giaccone G (1999) Current chemotherapeutic possibilities in pancreaticobiliary cancer. Ann Oncol 10:S157–S161
12. Moertel CG (1976) Chemotherapy of gastrointestinal cancer. Clin Gastroenterol 5:777–793

13. Ahlgren JD (1996) Chemotherapy for pancreatic carcinoma. Cancer 78:653–663
14. Rosemurgy AS, Serafini FM (2000) New directions in systemic therapy of pancreatic cancer. Cancer Control 7:437–451
15. Rosenberg L (2000) Pancreatic cancer: a review of emerging therapies. Drugs 59:1071–1089
16. Permert J, Hafstrom L, Nygren P, Glimelius B (2001) A systematic overview of chemotherapy effects in pancreatic cancer. Acta Oncol 40:361–370
17. Kozuch P, Petryk M, Evans A, Bruckner HW (2001) Treatment of metastatic pancreatic adenocarcinoma: a comprehensive review. Surg Clin North Am 81:683–690
18. Oettle H, Arnold D, Hempel C, Riess H (2000) The role of gemcitabine alone and in combination in the treatment of pancreatic cancer. Anticancer Drugs 11:771–786
19. Heinemann V (2001) Gemcitabine: progress in the treatment of pancreatic cancer. Oncology 60:8–18
20. Godefridus JP, Plunkett W (1995) Gemcitabine: status of preclinical studies and perspectives for the future clinical applications of this novel nucleoside analog. Semin Oncol 22 (Suppl 11):1–3
21. Guchelaar HJ, Richel DJ, Van Knapen A (1996) Clinical toxicological and pharmacological aspects of gemcitabine. Cancer Treat Rev 22:15–31
22. Casper ES, Green MR, Kelsen DP, Heelan RT, Brown TD, Flombaum CD, Trochanowski B, Tarassoff PG (1994) Phase II trial of gemcitabine (2,2′-difluorodeoxycytidine) in patients with adenocarcinoma of the pancreas. Invest New Drugs 12:29–34
23. Carmichael J, Fink U, Russell RCG, Spittle MF, Harris AL, Spiessi G, Blatter J (1996) Phase II study of gemcitabine in patients with advanced pancreatic cancer. Br J Cancer 73:101–105
24. Crino L, Mosconi AM, Calandri C, Corgna E, Darwish S, Tonato M (1997) Gemcitabine in advanced pancreatic cancer: a phase II trial (abstract). Eur J Cancer 33:1266
25. Crino L, Mosconi AM, Calandri C, Corgna E, Porrozzi S, Chiara S, Nobili MT, Tonato M (2001) Gemcitabine in advanced pancreatic cancer: a phase II trial. Am J Clin Oncol-Cancer Clinical Trials 24:296–298
26. Aykan F, Argon A, Alici S, Bulutlar G (2000) A phase II trial of gemcitabine in patients with advanced pancreatic cancer (APC) (abstract). Proc Am Soc Clin Oncol 19:1241
27. Manzano H, Esquerdo G, Rita J, Agutar D, Arrivi A, Pazo R, Martin J, Terrasa J (1998) Clinical benefit with gemcitabine (GEM) as first-line therapy for patients with advanced pancreatic cancer (APC) (abstract). Ann Oncol 9 (Suppl 4):256
28. Petrovic Z, Jovic J, Perisic N, Brocic-Pecelj T (1998) Monotherapy with gemcitabine in patients with advanced pancreatic carcinoma (abstract). Ann Oncol 9 (Suppl 2):641
29. Kurtz JE, Trillet-Lenoir V, Bugat R, Negrier S, Adenis A, Kayitalire L, Ripoche V, Dufour P (1999) Compassionate use of gemcitabine in advanced pancreatic cancer: a French multicentric study. Bull Cancer 86:202–206
30. Meyer F, Hirbaschek A, Kuhn R, Eichelmann K, Luck A, Lippert H, Ridwelski K (2001) Antineoplastic effect and quality of life in patients with pancreatic carcinoma who received gemcitabine monotherapy. Viszeralchirurgie 36:85–90
31. Okada S, Ueno H, Okusaka T, Ikeda M, Furuse J, Mara Y (2001) Phase I trial of gemcitabine in patients with advanced pancreatic cancer. Jpn J Clin Oncol 31:7–12
32. Rothenberg ML, Moore MJ, Cripps MC, Andersen JS, Portenoy RK, Burris HA, Green MR, Tarassoff PG, Brown TD, Casper ES, Storniolo AM, Von Hoff DD (1996) A phase II trial of gemcitabine in patients with 5-FU-refractory pancreas cancer. Ann Oncol 7:347–353
33. Burris H, Storniolo AM (1997) Assessing clinical benefit in the treatment of pancreas cancer: gemcitabine compared to 5-fluorouracil. Eur J Cancer 33 (Suppl 1):s18–s22
34. Rothenberg ML, Abbruzzese JL, Moore M, Portenoy RK, Robertson JM, Wanebo HJ (1996) A rationale for expanding the endpoints for clinical trials in advanced pancreatic carcinoma. Cancer 78:627–632
35. Burris HA, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarssoff P, Nelson R, Dorr FA, Stephens CD, Von Hoff DD (1997) Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 15:2403–2413
36. Bramhall SR, Rosemurgy A, Brown PD, Bowry C, Buckels JAC (2001) Marimastat as first-line therapy for patients with unresectable pancreatic cancer: a randomized trial. J Clin Oncol 19:3447–3455
37. Moore MJ, Hamm J, Eisenberg P, Dagenais M, Hagan K, Fiels A, Greenberg B, Schwartz B, Ottaway J, Zee B, Seymour L (2000) A comparison between gemcitabine (GEM) and the matrix metalloproteinase (MMP) inhibitor BAY12-9566 (9566) in patients with advanced pancreatic cancer (abstract). Proc Am Soc Clin Oncol 19:930
38. Lersch C, Van Cutsem E, Amado R, Ehninger G, Heike M, Kerr D, Rothenberg ML, Baum CM, Zaknoen SL (2001) Randomized phase II study of SCH 66336 and gemcitabine in the treatment of metastatic adenocarcinoma of the pancreas (abstract). Proc Am Soc Clin Oncol 20:608
39. Di Costanzo F, Sdrobolini A, Carlini P, Massidda B, Mattioli R, Lop A, Barletta E, Moscetti L, Recchia F, Tralongo P, Ospedaliera A (2001) Gemcitabine (GEM) alone or in combination with 5-FU continuous infusion (CI) in the treatment of advanced pancreatic cancer (APC): a GOIRC randomized phase II trial (abstract). Proc Am Soc Clin Oncol 20:612
40. Berlin J, Catalano P, Thomas J, Kluger J, Haller D, Benson AB (2001) A phase III study of gemcitabine in combination with 5-FU vs gemcitabine alone in patients with advanced pancreatic carcinoma (E2297): an Eastern Cooperative Oncology Group (ECOG) trial (abstract). Proc Am Soc Clin Oncol 20:505
41. Colucci G, Riccardi F, Giuliani F, Lopez V, Gebbia V, Uomo G, Biglietto M, Cigolari S, Borsellino N, Paoletti G, Mainello E, Gebbia N (1999) Randomized trial of gemcitabine (GEM) alone or with cisplatin (CDDP) in the treatment of advanced pancreatic cancer (APC): a phase II multicenter study of the Southern Italy Oncology Group (abstract). Proc Am Soc Clin Oncol 18:961
42. Heinemann V, Quietzsch D, Gieseler F, Schonekas H, Rost A, Neuhaus H, Clemens M, Szymala M, Hiddemann W, Schalhorn A, Grosshadern K (2001) Gemcitabine plus cisplatin versus gemcitabine in advanced pancreatic cancer: preliminary results of a randomized phase III trial (abstract). Proc Am Soc Clin Oncol 20:625
43. Storniolo AM, Enas NH, Brown CA, Enas NH, Brown CA, Vol M, Rothenberg ML, Schilski R (1999) An investigational new drug treatment for patients with gemcitabine. Cancer 85:1261–1268
44. Brand R, Capadano M, Tempero M (1997) A phase I trial of weekly gemcitabine administered as a prolonged infusion in patients with pancreatic cancer and other solid tumors. Invest New Drugs 15:331–341
45. Tempero M, Plunkett W, Ruiz van Haperen V, Hainsworth J, Hochster H, Lenzi R, Abbruzzese J (1999) Randomized phase II trial of dose intense gemcitabine by standard infusion vs fixed dose rate in metastatic pancreatic adenocarcinoma (abstract). Proc Am Soc Clin Oncol 18:1048
46. Fossella FY, Lippman SM, Shin DM, Tarassoff P, Calayag-Jung M, Perez-Soler R, Lee JS, Murphy WK, Glisson B, Rivera E, Hong WK (1997) Maximum-tolerated dose defined for single-agent gemcitabine: a phase I dose-escalation study in chemotherapy-naïve patients with advanced non-small cell lung cancer. J Clin Oncol 15:310–316

47. Ulrich-Pur H, Kornek GV, Raderer M, Haider K, Kwasny W, Depisch D, Greul R, Schneeweiss B, Krauss G, Funovics J, Schelthauer W (2000) A phase II trial of biweekly high dose gemcitabine for patients with metastatic pancreatic adenocarcinoma. Cancer 88:2505–2511
48. Spagnuolo P, Roversi R, Rossi G, Ricci S, Calandri C, Cavallo G, Marrocolo F, Crino L (1999) Phase II study of gemcitabine as locoregional treatment of advanced pancreatic cancer (abstract). Proc Am Soc Clin Oncol 18:1153
49. Weissmann A, Ludwig H (1999) Intraarterial gemcitabine for treatment of inoperable pancreatic and cholangiocarcinoma (abstract). Proc Am Soc Clin Oncol 18:1170
50. Hidalgo M, Castellano D, Paz-Ares L, Alonso S, Diaz-Puente M, Catellanos D, Cortes-Funes H (1999) A phase I–II study of gemcitabine and fluorouracil as a continuous infusion in patients with pancreatic cancer. J Clin Oncol 17:585–592
51. Cascinu S, Silva RR, Barni S, Labianca R, Frontini L, Piazza E, Pancera G, Giordani P, Giuliodori L, Pessi MA, Fusco V, Luporini G, Cellerino R, Catalano G (1999) A combination of gemcitabine and 5-fluorouracil in advanced pancreatic cancer, a report from the Italian Group for the Study of Digestive Tract Cancer (GISCAD). Br J Cancer 80:1595–1598
52. Louvet C, Hammel P, Andre Vanica R, Landi B, Balosso J, Cattan S, Fonck M, Flesch M, Colin P, Gruson T (1999) Multicenter phase II study in advanced pancreatic adenocarcinoma patients treated with a combination of leucovorin, 5-FU bolus and infusion, and gemcitabine (FOLFUGEM Regimen) (abstract). Proc Am Soc Clin Oncol 18:1054
53. Riedel C, Wein A, Wehler M, Lampert S, Fischer B, Hohenberger W, Hahn EG, Schneider T (2000) High-dose fluorouracil (FU) 24-h-infusion with gemcitabine (GEM): tolerable and efficient in palliative outpatient treatment of pancreatic cancer (abstract). Proc Am Soc clin Oncol 19:1248
54. Berlin JD, Adak S, Vaughn DJ, Flinker D, Blaszkowsky L, Harris JE, Benson AB III (2000) A phase II study of gemcitabine and 5-fluorouracil in metastatic pancreatic cancer: an Eastern Co-operative Group Study (E 3296). Oncology 58:215–218
55. Peters GJ, Bergman AM, Ruiz van Haperen VW, Veerman G, Kuiper CM, Braakhuis BJ (1995) Interaction between cisplatin and gemcitabine in vitro and in vivo. Semin Oncol 22 (4 Suppl 11):72–79
56. Bergman AM, Ruiz van Haperen VW, Veerman G, Kuiper CM, Peters GJ (1996) Synergistic interaction between cisplatin and gemcitabine in vitro. Clin Cancer Res 2:521–530
57. Sandler AB, Nemunaitis J, Denham C, Von Pawel J, Cormier Y, Gatzemeier U, Mattson K, Manegold CH, Palmer MC, Gregor A, Nguyen B, Niyikiza C, Einhorn LH (2000) Phase III trial of gemcitabine plus cisplatin versus cisplatin alone in patients with locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 18:122–130
58. Von der Maase H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, Bodrogi I, Albers P, Knuth A, Lippert CM, Kerbrat P, Sanchez Rovira P, Wersall P, Cleall SP, Roychowdhury DF, Tomlin I, Visseren-Grul CM, Conte PF (2000) Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol 18:3068–3077
59. Nagourney RA, Link JS, Blitzer JB, Forsthoff C, Evans SS (2000) Gemcitabine plus cisplatin repeating doublet therapy in previously treated, relapsed breast cancer patients. J Clin Oncol 18:2245–2249
60. Heinemann V, Wilke H, Possinger K, Mergenthaler K, Clemens M, Konig HJ, Illiger HJ, Ohnmacht U, Arning M, Schalhorn A, Fink U (1999) Gemcitabine and cisplatin in the treatment of advanced and metastatic pancreatic cancer: final results of a phase II study (abstract). Proc Am Soc Clin Oncol 18: 1052
61. Philip PA, Zalupski M, Vaitkevicius VK, Arlauskas P, Shields A (1999) Phase II study of gemcitabine and cisplatin in advanced or metastatic pancreatic cancer (abstract). Proc Am Soc Clin Oncol 18:1053
62. Klapdor R, Scutter E, Lang-Polckow EM, Reichle H, Hinrichs A (1997) Locoregional systemic chemotherapy of locally advanced/metastasized pancreatic cancer with a combination of mitomycin-C and gemcitabine and simultaneous follow-up by imaging methods and tumor markers. Anticancer Res 17:4230–4231
63. Bazin I, Garin A, Bulat J, Zharkov S, Popov A (1998) Preliminary results of gemzar+mitomycin in treatment of advanced pancreatic cancer (abstract). Ann Oncol 9(Suppl 2):681
64. Carmichael J, Ledermann JD, Woll PJ, Gulliford T, Russell RC (1998) Phase Ib study of concurrent administration of marimastat and gemcitabine in non-resectable pancreatic cancer (abstract). Proc Am Soc Clin Oncol 17:888
65. Kath R, Hoffken K, Raida M, Haus U, Schneider O, Schmiegel W, Graeven U (1998) Phase II trial of high dose continuous octreotide infusion (hdcoi) and gemcitabine (gm) in advanced pancreatic cancer (pc) (abstract). Ann Hematol 77(Suppl 2):S48
66. Raderer M, Kornet GV, Valencak J, Lenauer A, Fleblger W, Greul R, Lang F, Schneeweiss B, Depisch D, Scheithauer W (1998) Phase II trials of gemcitabine, epirubicin, and G-CSF in patients with metastatic pancreatic cancer (abstract). Ann Oncol 9(Suppl 2):169
67. Tomao S, Ionta MT, Romiti A, Nicolosi P, Di Seri M, Mozzicafreddo A, Massidda B (1998) Gemcitabine (GEM) and tamoxifen (TAX) in patients with advanced pancreatic cancer (APC). Impact on quality of life of an innovative association (abstract). Ann Oncol 9(Suppl 2):682
68. White JD, Carmichael J, Woll PJ, Guilford T, Russell RC (1998) Phase 1B study of concurrent administration of marimastat and gemcitabine in nonresectable pancreatic cancer (abstract). Br J Cancer 79(Suppl 3):P07
69. Bazin I, Garin A, Bulat J, Narimanov M, Nosov D, Titov D, Popov A, Nasyrova R, Tiulandin S (1999) Gemzar (GEM)+mitomycin C (MMC) in patients with advanced pancreatic cancer (APC) (abstract). Eur J Cancer 35(Suppl 4):556
70. Caillouette C, Hammond LA, Razvillas B, Baughman C, Campbell A, Linnartz R, Kay AC, Rothenberg ML (1999) A phase I/II trial of SMS 201-995 pa LAR (SMS pa LAR) and gemcitabine in patients with advanced pancreatic cancer (abstract). Proc Am Soc Clin Oncol 18:1071
71. Kakolyris S, Stathopoulos G, Tsavaris N, Andoroulakis N, Kouroussis Ch, Samantas E, Dimopoulos AM, Fountzilas G, Sarra E, Hatzidaki D, Samonis, Georoulias V (1999) First-line treament with docetaxel (D) and gemcitabine (G) in patients with advanced pancreatic cancer: a multicenter phase II study (abstract). Proc Am Soc Clin Oncol 18:960
72. Klapdor R, Martini-Svendsen J, Seuttler R, Fenner C (1999) Combination therapy with oxaliplatin+gemcitabine in advanced pancreatic cancer (abstract). Eur J Cancer 35:536
73. Neri B, Mini E, Fioretto L, Francesconi D, Medi F (1999) Dose-finding study of gemcitabine and epirubicin in patients with advanced pancreatic cancer (abstract). Proc Am Soc Clin Oncol 18:1128
74. Reni M, Ferreri AJM, Panucci MG, Cordio S, Scaglietti U, Ceresoli GL, Bordogna G, Garassino M, Villa E, Ratraele H (1999) Significant improvement of response rate and survival with cisplatin, epirubicin, 5-fluorouracil and gemcitabine (PEF-G regimen) in metastatic pancreatic cancer (abstract). Eur J Cancer 35(Suppl 4):547
75. Villa E (1999) PEF-G (cisplatin, epirubicin, 5-fluorouracil continuous infusion, gemcitabine): a new combination in advanced pancreatic adenocarcinoma. Phase II study (abstract). Proc Am Soc Clin Oncol 18:1055
76. Clark JW, Ryan DP, Kulki MH, Grossbard ML, Fuchs CS, Grossman SR, Morgan JA, Earle CC, Shivdasani R, Grenon N,

Berg D, Mayer RJ (2000) Phase II study of gemcitabine and docetaxel in patients with metastatic pancreatic cancer (abstract). Proc Am Soc Clin Oncol 19:1238
77. Herrmann R, Borner M, Morant R, Roth AD, Ludwig C, Bedoucha V (2000) Combining gemcitabine (GEM) and capecitabine (CAP) in advanced pancreatic cancer. Results of a phase I trial(abstract). Proc Am Soc Clin Oncol 19:1038
78. Rocha Lima D, Savarese H, Bruckner A, Dudek A, Eckardt J, Hainsworth J, Lester E, Compton L, Locker P, Elfring G, Miller L, Green M (2000) Multicenter phase II trial of first-line irinotecan and gemcitabine (Iriongem) in patients with locally advanced or metastatic pancreatic cancer (PC) (abstract). Proc Am Soc Clin Oncol 19:1023
79. Stathopoulos G, Rigatos G, Dimopoulos M, Kouroussis C, Panopoulos C, Giannakakis T, Tzannisis D, Georgoulias V (2000) Front-line treatment of pancreatic carcinoma with gemcitabine in combination with irinotecan (CPT-11): preliminary results of a multicentre phase II study (abstract). Proc Am Soc Clin Oncol 19:1260
80. Shewach DS, Lawrence TS (1995) Radiosensitization of human tumor cells by gemcitabine in vitro. Semin Oncol 22(Suppl 11):68–71
81. Lawrence TS, Davis MA, Hough A, Rehemtulla A (2001) The role of apoptosis in 2′,2′-difluoro-2′-deoxycytidine-(gemcitabine)-mediated radiosensitization. Clin Cancer Res 7:314–319
82. Doyle TH, Mornex F, Gillies McKenna W (2001) The clinical implications of gemcitabine radiosensitization. Clin Cancer Res 7:226–228
83. McGinn CJ, Smith DC, Szarka C, Pinover WH, Loehrer PJ, Morphis JG, Nicol S, Shewach DS, Lawrence TS, O'Dwyer PJ (1998) A phase I study of gemcitabine in combiantion with radiation therapy in patients with localized, unresectable pancreatic cancer (abstract). Proc Am Soc Clin Oncol 17:1014
84. Wolff RA, Evans DB, Gravel DM, Lenzi R, Pisters PW, Lee JE, Janjan NA, Goswitz MS, Abbruzzese JL (1998) Phase I trial of gemcitabine combined with radiation for the treatment of locally advanced pancreatic adenocarcinoma (abstract). Proc Am Soc Clin Oncol 17:1091
85. Abad A, Arellano A, Brunet J, Balart J, Navarro M, Cambray M, Cervantes A, Insa A, Anton A, Tres A (1998) Gemcitabine plus radiotherapy in stage II–III pancreatic cancer: a phase I trial (abstract). Ann Oncol 9:253
86. Brierley J, Oza A, Pantnaik A, Wong CS, Siu L, Gallinger S, Langer B, Martha M, Moore M (1999) A phase I study of radiation therapy and gemcitabine in patients with locally advanced pancreatic carcinoma (abstract). Proc Am Soc Clin Oncol 18: 713
87. Wong S, Oza AM, Brierley J, Siu A, Patnaik A, MacLean M, Gallinger S, Langer N, Moore M (2000) Phase I study of gemcitabine (G) and escalating dose radiation therapy (RT) in patients with pancreatic carcinoma (abstract). Proc Am Soc Clin Oncol 19:1041
88. Herscher LL, Muir M, Kroog GS, Cook JA, Michell JB (2000) A Phase I trial of gemcitabine and radiation in locally advanced unresectable cancer of the pancreas (abstract). Proc Am Assoc Cancer Res 41:3898
89. Epelbaum R, Rosenblatt E, Nasrallah S, Muler E, Yardeni T, Faraggi D, Kopelman D, Mizrahi S, Kuten A (2000) Phase II study of gemcitabine (GEM) combined with radiation therapy (RT) in patients with localized, unresectable pancreatic cancer (abstract). Proc Am Soc Clin Oncol 19:1029
90. Blackstock AW, Tempero MA, Niedwiecki D, Hollis DE, Mayer RJ, Tepper JE (2001) Cancer and Leukemia Group B (CALGB) 89805: phase II chemoradiation trial using gemcitabine in patients with locoregional adenocarcinoma of the pancreas (abstract). Proc Am Soc Clin Oncol 20:627
91. Mustacchi G, Beorchia A, Milani S, Ceccherini R, Amoroso V, Marcuzzi S, Ceschia T, Milan V, Vidali C (2001) Gemcitabine (Gem) and concomitant radiation for locally advanced or relapsed pancreatic cancer (abstract). Proc Am Soc Clin Oncol 20:2288
92. Maurer U, Segmeier P, Boite R, Jungius KP, Mueller D, Georgi M (1999) Gemcitabine (G) in combination radiation therapy (RT) in stage III-IV pancreatic cancer: first results of a current phase I study (abstract). Eur J Cancer 35(Suppl 4):544
93. Reyes-Vidal JM, Rodriguez PA, Reyes J, Buckel E, Veit O, Orlandi L, Baeza R (2000) Chemoradiation therapy with gemcitabine (GEM) in advanced pancreatic cancer (APC) (abstract). Proc Am Soc Clin Oncol 19:1183
94. McGinn CJ, Zalupski MM, Shureiqi I, Robertson JM, Eckhauser FE, Smith DC, Decker DA, Neumann KH, Brown D, Hejna G, Strawderman M, Mormolle D, Lawrence TS (2001) Final report of phase I trial of radiation (RT) dose escalation with concurrent weekly full dose gemcitabine (Gem) in advanced pancreatic cancer (abstract). Proc Am Soc Clin Oncol 20: 609
95. Antonisse IE, Van Groeningen CJ, Langendijk JA, Slotman BJ (1999) A phase II study of hypofractionated radiotherapy in combination with gemcitabine in the palliative treatment of advanced pancreatic carcinoma (abstract). Eur J Cancer 35(Suppl 4):514
96. Blackstock AW, Bernard S, Poole M, Richards F, Tepper JE (2000) Concurrent radiation and twice weekly gemcitabine for unresectable pancreatic cancer. Cancer Invest 18:1:24–26
97. Wolff RA, Madary AR, Pisters PWT, Lee JE, Lenzi R, Vauthey JN, Janjan NA, Crane CH, Staley C, Termuhlen P, Cleary K, Charnsangave C, Abbruzzese JL, Evans DB (1999) Pre-operative gemcitabine and radiation for resectable adenocarcinoma of the pancreas. Preliminary report of a phase II multi institution trial (abstract). Clin Cancer Res 5(Suppl):225
98. Hoffmann JP, McGinn CJ, Ross E, Litwin S, Szarka C, Morphis J, Cooper HS, Wilkes J, O'Dwyer P, Nicol S (1999) A phase I trial of preoperative gemcitabine and radiotherapy followed by postoperative gemcitabine for patients with localized, resectable pancreatic adenocarcinoma. Cancer Invest 17(Suppl):30–32
99. Lange SM, Groeningen CJ, Giaccone G, Pinedo HM, Meijer OWN, Langeddijk JA, Slotman BJ (2000) Gemcitabine-radiotherapy in patients with locally advanced pancreatic cancer (abstract). Clin Cancer Res 6(Suppl):371
100. Hietaniemi K, Kärkkäinen P, Kiviluoto T, Kivisaari L, Elomaa, I, Joensuu T (2001) Phase I-II trial of twice-weekly gemcitabine (GEM) and concomitant irradiation in patients (Pts) with locally advanced pancreatic cancer (abstract). Proc Am Soc Clin Oncol 20:2318
101. Kachnic LA, Mornex F, Partensky C (2001) Phase II trial of twice-weekly gemcitabine and concurrent radiation for the treatment of resected pancreatic cancer (abstract). Proc Am Soc Clin Oncol 20:2334
102. van Laethem JL, Gay F, Danhier S, Colette M, Houbiers G, Closon M, Houtte PV, Closset J (2001) Postoperative adjuvant gemcitabine (GEM) and GEM + concurrent radiation for resected pancreatic adenocarcinoma: a feasibility phase II study (abstract). Proc Am Soc Clin Oncol 20:611
103. Lee NC, Bouvet M, Nardin S, Jiang P, Baranov E, Radhidi B, Yang M, Wang X, Moossa AR, Hoffma RM (2001) Antimetastatic efficacy of adjuvant gemcitabine in a pancreatic cancer orthotopic model. Clin Exp Metastasis 18:379–384
104. Friedman NS, Brenner MJ, Linder JA, Bosley JA, Burdick RK, Didolkar MS (1999) Adjuvant radiation and continuous 5-FU followed by gemcitabine as adjuvant treatment for resected pancreatic cancer (abstract). Proc Am Soc Clin Oncol 18:1089
105. Kachnic LA, Shaw JE, Manning MA, Lauve AD, Neifeld JP (2001) Gemcitabine following radiotherapy with concurrent 5-fluorouracil for nonmetastatic adenocarcinoma of the pancreas. Int J Cancer 96:132–139

106. Oettle H, Arning M, Langrehr J, Schramm H, Ridwelski K, Post S, Neuhaus P, Riess H (2001) A randomized study of gemcitabine (GEM) versus observation as adjuvant treatment for pancreatic cancer. Results of an interim safety analysis (abstract). Proc Am Soc Clin Oncol 20:2335
107. Sasson AR, Wetherington RW, Hoffman JP, Ross E, Cooper HS, Meropol NJ, Freedman G, Pingpank JF, Eisenberg BL (2001) Neoadjuvant therapy for adenocarcinoma of the pancreas: histopathologic effect and analysis of outcome (abstract). Proc Am Soc Clin Oncol 20:621
108. Heinemann V, Schermuly MM, Stieber P, Schulz L, Jungst D, Wilkowski R, Schalhorn A (1999) CA 19-9: A predictor of response in pancreatic cancer treated with gemcitabine and cisplatin. Anticancer Res 19:1–3
109. Wiernik PH (2000) Current status of and future prospects for the medical management of adenocarcinoma of the exocrine pancreas. J Clin Gastroenterol 30:357–363
110. Gunzburg WH, Salmons B (2001) Novel clinical strategies for the treatment of pancreatic carcinoma. Trends Mol Med 7:30–37