Review

Oncology

Oncology 2001;60:8–18

Gemcitabine: Progress in the Treatment of Pancreatic Cancer

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Key Words

Clinical benefit response · Combination therapy · Gemcitabine · Palliative chemotherapy · Pancreatic cancer · Single agent · Tumor marker

Abstract

Unresectable pancreatic cancer has a dismal prognosis with a median survival of 3–5 months in untreated disease. Since the introduction of gemcitabine, pancreatic cancer may no longer be regarded a chemotherapy-resistant tumor. Treatment with single-agent gemcitabine achieved clinical benefit and symptoms improvement in 20–30% of patients. While 1-year survival was observed in 2% of 5-fluorouracil (5-FU)-treated patients, it was raised to 18% by single-agent gemcitabine. Good treatment tolerability and low incidence of side effects are clear advantages of single-agent gemcitabine. Improvement of efficacy is, however, expected from combination treatment. Gemcitabine and cisplatin given as first-line treatment in three studies achieved a median survival of 7.4–8.3 months. One-year survival was raised to 28% as reported in one study. Comparable activity was obtained by a combination of gemcitabine with 5-FU. Nine studies using gemcitabine in combination with standard-dose or high-dose 5-FU reported a median survival ranging from 5.5 to 13 months. Notwithstanding these promising results, recommendations regarding palliative chemotherapy of pancreatic cancer remain tentative and still need confirmation by presently ongoing phase III trials. Inclusion of pancreatic cancer patients into clinical trials should be a major goal. Outside clinical trials, patients should present with an adequate PS (Karnofsky-performance index ≥ 70) to qualify for chemotherapy.

Introduction

The incidence of pancreatic cancer has risen in recent decades. Cancer of the pancreas currently ranges between the fourth and the fifth leading cause of cancer mortality [1, 2]. The disease primarily involves an older population with a peak incidence in the sixth decade. Tumors predominantly evolve from the exocrine pancreas and represent adenocarcinomas in 95% of cases.

The inherent dilemma of pancreatic carcinoma consists in an early systemic spread and a late diagnosis. Most of patients (85–90%) are diagnosed at an advanced stage when curative surgery is no longer possible. Thus, the great majority of patients will eventually succumb to metastatic disease, with a median survival of 3–6 months [3]. Given this situation, an improvement of prognosis may

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only be expected from an optimization of systemic treatment.

Response to chemotherapy is greatly dependent on the performance status (PS) of the patient. A Karnofsky PS ≥ 70 was associated with a survival time more than 2-fold longer (5.5 months) than that in patients with lower PS values (2.4 months) [4]. Disease stage is another important prognostic parameter [4], as patients with locally advanced tumors demonstrated a longer median survival (6.6 months) compared to that of patients with metastatic disease (4.4 months). Therefore, the relative risks and potential benefits of systemic chemotherapy should be weighed in each situation to ensure that patients and physicians have realistic expectations regarding treatment.

Evaluation of Response in Pancreatic Cancer

Even modern imaging techniques, such as computed tomography (CT) or magnetic resonance imaging (MRI), frequently do not allow accurate localization and measurement of tumor extension within the adjacent tissues [2]. This is partly explained by the retroperitoneal localization of pancreatic tumors. Additionally, desmoplastic and local inflammatory reactions induced by the tumor make it difficult to differentiate between tumor and normal surrounding tissue. Differences in response between metastatic lesions and primary tumor may be explained on grounds of variable desmoplastic reactions. Tumor response may be underestimated because reactive fibrous tissue does not readily shrink during successful chemotherapy. By contrast, inflammatory reactions may be reduced more rapidly causing an overestimation of tumor response [5].

Consequently, there is not only a problem of tumor size definition at the time of diagnosis, but also a frequently inadequate estimation of tumor response when chemotherapy has been applied [6]. Conventional endpoints such as tumor response may therefore be inadequate tools for the evaluation of pancreatic cancer treatment.

Endpoints of Palliative Chemotherapy in Pancreatic Cancer

Because tumor response occurs late during treatment and may be obscured by diagnostic uncertainties, new endpoints have to be determined. Stabilization of disease should be accepted as the primary goal of palliative treatment, which can best be expressed by the combined evaluation of complete response (CR) + partial response (PR) + stable disease (SD). Even patients with SD respond to treatment and may ultimately profit from it by prolonged survival.

The determination of 1-year survival in addition to median survival appears to be a useful tool to characterize those patients who show a prolonged treatment benefit. Because there is a large amount of poorly responding pancreatic cancer patients, 1-year survival provides superior information about the responding minority.

Analysis of Clinical Benefit Response as a Surrogate Parameter for Response

A reduction of quality-of-life symptoms has gained increasing interest as a surrogate parameter of tumor response [5]. Specific attention has been given to the reduction of pain and analgesic consumption. Tumor-associated pain caused by irritation of the splanchnic nerve is a leading symptom of pancreatic cancer (80% at first diagnosis). Clinical experience shows that small reductions of tumor size, objectively corresponding to SD, may often cause a major improvement of pain. Amelioration of tumor-associated pain often precedes the measurable reduction of tumor size and consequently serves as an early predictor of therapeutic efficacy [7].

Consequently, a number of studies have analyzed 'clinical benefit response' as a composite parameter of clinical efficacy [8, 9]. Two primary measures were evaluated: the *first measure* consisted of the parameters, PS and pain; the latter being composed of pain intensity and analgesic consumption. The course of the patient's body weight was analyzed as a *second measure*. Clinical benefit response was then primarily evaluated using the parameters of pain and PS. Weight gain was additionally used only if a patient was considered stable by primary measures. A positive response of clinical benefit was established when a significant improvement from baseline of the respective measures was observed for an interval of at least 4 weeks: pain intensity $\leq 50\%$, analgesic consumption $\leq 50\%$, improvement of Karnofsky PS by ≥ 20 points, or weight gain $\geq 7\%$ [9].

Table 1. 5-Fluorouracil: efficacy in three independent randomized trials

Reference	5-FU regimen	n/eval	PR, %	SD, %	Survival months	1-year survival, %
16	500 mg/m^2, d 1–5 q 5 weeks	64/41	7	NA	3.5	NA
8	600 mg/m^2, weekly	63/57	0	19	4.41	2
15	500 mg/m^2, d 1–5 q 4 weeks	103/97	0	13.4	NA	9

n/eval = Recruited/evaluable patients; 5-FU = 5-fluorouracil; PR = partial remission; SD = stable disease; NA = not available.

Tumor Marker CA 19-9: A Parameter of Tumor Response

In view of everyday decision making, analysis of surrogate constructs like quality of life (QOL), symptoms reduction, or clinical benefit are time consuming and frequently lack objectivity. Alternatively, determination of tumor marker kinetics may provide simple, fast, and reliable information on therapeutic efficacy.

The prognostic importance of CA19-9 has already been demonstrated for neoadjuvant treatment of operable pancreatic cancer [10–13]. Due to the rather low activity of chemotherapy, data have remained scarce regarding the impact of CA19-9 kinetics during palliative treatment. In a study using gemcitabine and cisplatin for palliative treatment, 20 of 21 evaluable patients presented with elevated tumor markers. All patients responding to chemotherapy with a CR or PR (8/21) demonstrated a fast and lasting reduction of CA19-9. Although the decline of CA19-9 was observed after the first treatment cycle, remissions were documented by imaging procedures only after a median of five chemotherapy courses. However, only patients reaching CR (4/21) achieved normalization of CA19-9 levels. In patients where SD was determined by imaging techniques, CA19-9 declined in all but one patient (7/8), demonstrating the biochemical efficacy of treatment without significant reduction of tumor volume. These data indicate that determination of CA19-9 may provide additional reliable evidence of response, however, a prospective, randomized trial is necessary before it is clear that CA19-9 could help guide clinical decision making and ultimately reduce the number of imaging procedures necessary. Its role in the majority of patients with pancreatic cancer who do not have an objective response to therapy, but rather may experience palliation of symptoms, also remains unclear [14].

Palliative Chemotherapy: Single-Agent and Combination Regimens

Since curative therapeutic approaches are not available, therapeutic efforts in tumor stages III and IV are mainly directed towards palliation. In the past, pancreatic cancer was rightfully considered a chemo- and radio-resistant tumor. A recent analysis of 28 phase II trials (1991–1994) analyzing the efficacy of 25 different agents demonstrated a median objective response rate (RR) of 0% (range 0–14.3%), while median survival in 19 evaluable studies amounted to 3 months (range 2–8.3 months) [5]. Thus, based on these data, the benefit of chemotherapy as an instrument for disease palliation is clearly questionable.

Accordingly, a generally accepted chemotherapy regimen had not been defined for pancreatic cancer. 5-Fluorouracil (5-FU) was frequently the drug of choice when single-agent chemotherapy was used in selected patients. While high RRs in the range of 15–20% were reported in the 1970–1980s, more recent analyses, performed in the 1990s, confirmed a median response rate of only 0–14%. The true importance of 5-FU treatment may be demonstrated more adequately by an analysis of three randomized studies (table 1). Taken together, 207 patients received either single-agent 5-FU [8, 15] or 5-FU/folinic acid [16]. While two studies reported an RR of 0% [8, 15], the other [16] showed a response in 7% of patients, yielding a mean remission rate for the three studies of 2.3%. In two evaluable studies, median survival was 3.5 and 4.65 months, respectively, and clearly did not exceed the survival expected with best supportive care alone [8, 16]. New agents, such as paclitaxel, docetaxel, irinotecan, topotecan, and oxaliplatin, have been tested in pancreatic cancer, but have not gained clinical importance so far.

Table 2. Studies of gemcitabine single-agent activity in pancreatic carcinoma

Reference	Phase	n/eval	Treatment	Gemcitabine dose, mg/m^2	PR n (%)	SD n (%)	PR + SD %	Clinical benefit response eval/n (%)	Survival months
19	II	44/35	1st-line	800	5 (14.3)	14 (40.0)	54.3	NA	5.6
18	II	34/32	1st-line	800	2 (6.3)	6 (18.8)	25.1	NA	6.3
8	III	63/56	1st-line	1,000	3 (5.4)	22 (39.3)	44.7	15/63 (23.8)	5.7
9	II	63/57	5-FU-refractory	1,000	6 (10.5)	17 (29.8)	40.3	17/63 (27.0)	3.9

n/eval = Recruited/evaluable patients; 5-FU = 5-fluorouracil; PR = partial remission; SD = stable disease; NA = not available.

Combination regimens like FAM (5-FU, doxorubicin, mitomycin C) or SMF (streptozotocin, mitomycin C, 5-FU) have induced higher RRs at the expense of greater toxicity. A prolongation of survival compared to that of single-agent 5-FU was, however, not achieved in randomized studies [3, 16].

Single-Agent Activity of Gemcitabine in Advanced Pancreatic Cancer

Gemcitabine is a pyrimidine antimetabolite [17] with good activity in various solid tumors and is presently recommended as a first-line treatment in pancreatic cancer. The typical phase II regimen of single-agent use includes a dose of 1,000–1,200 mg/m^2 given as a 30-min i.v. infusion on days 1, 8, and 15 of a 28-day cycle [3]. Gemcitabine is characterized by a low profile of side effects and accordingly by an excellent clinical tolerability.

Currently, four studies – one randomized, pivotal phase III study [8] and three phase II studies [9, 18, 19] – are available demonstrating the clinical activity of gemcitabine in pancreatic cancer (table 2). A consequent analysis of clinical benefit response was performed in two studies [8, 9]. Only those patients with the following were included: a Karnofsky PS <80, a pain intensity score ≥ 20 mm (of a possible 100 mm according to the Memorial Pain Assessment Card), or a baseline analgesic consumption of ≥ 10 mg morphine equivalent per day. The following conclusions may be drawn from the summary of the results of these two studies. A clinical benefit response was observed in 24 and 27%, respectively, of gemcitabine-treated patients [8, 9] and exceeded the clinical benefit of 5-FU treatment (4.8%) as observed in the randomized study ($p = 0.0022$) [8]. Accordingly, the median survival of gemcitabine-treated patients was also significantly longer than that of the 5-FU-treated patients ($p = 0.0025$). After a follow-up of 1 year, 18% of gemcitabine-treated patients survived compared to 2% of 5-FU-treated patients [8]. With a PR rate of 5.4–14.3%, the objective response may be considered moderate. If, however, SD and PR are taken together as an acceptable goal of palliative treatment, the objective rate of disease stabilization (25.1–54.3%) fits the results of the clinical benefit response evaluation much better.

Within an investigational new drug treatment program analyzing 3,023 pancreatic cancer patients treated with single-agent gemcitabine, a prospective evaluation of disease-related symptoms improvement yielded a cumulative rate of 18.4% after the fourth treatment cycle. In 982 evaluable patients, an overall RR of 12% (95% confidence interval [CI], 10.0–14.0%) was noted. For 2,380 patients with evaluable survival data, median survival was 4.8 months (95% CI, 4.5–5.1 months) with a 1-year survival of 15% [4].

High-Dose Gemcitabine and Prolonged Drug Application

While a gemcitabine dose of 1,000–1,200 mg/m^2 applied as a 30-min infusion has become a widely accepted standard for single-agent treatment, the optimal dose has not been defined so far. Fossella et al. [20] performed a phase I study in first-line non-small cell lung cancer (NSCLC) patients evaluating gemcitabine doses ranging from 1,000–2800 mg/m^2. In this patient entity, a maximum tolerated dose of 2,200 mg/m^2/week for 3 weeks every 4 weeks was reported.

Table 3. Gemcitabine plus cisplatin combination treatment in phase II studies

Reference	n/eval	Regimen	OR, %	SD, %	Survival months
27	41/35	Gemcitabine 1,000 mg/m^2, d 1, 8, 15 Cisplatin 50 mg/m^2, d 1, 15, q d 29	11.4	57.1	8.3
29	52/32	Gemcitabine 1,000 mg/m^2, wkly × 7 Cisplatin 25 mg/m^2, wk 1–3 and 5–7, then 1 wk rest, then d 1, 8, 15 q d 29	31	NA	NA
28	27/22	Gemcitabine 1,000 mg/m^2, d 1, 8, 15 Cisplatin 50 mg/m^2, d 1, 15, q d 29	36.4	27.3	7.4
38	49/43	Gemcitabine 600 mg/m^2, d 1 + 8 Cisplatin 40 mg/m^2, d 1 Epirubicin 40 mg/m^2, d 1 5-FU CI 200 mg/m^2, d 1–28, q 4 weeks	58	33	9.4+

n/eval = Recruited/evaluable patients; 5-FU = 5-fluorouracil; OR = overall remission; SD = stable disease; NA = not available; CI = continuous infusion.

Pur et al. [21] undertook a phase II study in metastatic pancreatic cancer patients applying gemcitabine at the increased dose of 2,200 mg/m^2 every 2 weeks. In 39 evaluable patients, a PR rate of 22.5%, an SD rate of 40%, and a median survival of 7.3 months were reported. Clinical benefit was observed in 37% (11/30) of patients. These data would argue for a dose increase of gemcitabine, because comparable treatment results have not been achieved with standard doses in the range of 800–1,000 mg/m^2 (table 2).

However, these data need to be discussed in the context of the results of the following randomized phase II trial of dose-intense gemcitabine by Tempero et al. [22]. In the standard infusion arm (A), gemcitabine was administered to 37 patients with metastatic disease at a dose of 2,200 mg/m^2 (30-min. i.v. infusion) weekly times three every 4 weeks. While dose intensity was greater in this trial, the RR was only 2.7% with a median survival of 4.7 months and a 1-year survival of 0%. These results are not only in striking contrast to the results published by Pur et al., they also do not fit into the context of the data so far reported for single-agent gemcitabine as shown in table 2. The comparator arm (B) of this trial investigated the efficacy of a fixed gemcitabine dose rate of 10 mg/m^2 per minute. This dose rate was chosen because previous studies had demonstrated saturation of the activating enzyme deoxycytidine kinase. Thirty patients received 1,500 mg/m^2 as a 150-min infusion. This schedule resulted in an RR of 16.6%, a median survival of 6.1 months, and a 1-year survival of 23%. The promising activity achieved with the fixed dose rate in arm B seems to support the underlying pharmacologic mechanism; however, the need for confirmatory phase III trials is clearly needed, and no definitive conclusions may be drawn at the present time.

Combination Therapy with Gemcitabine and Cisplatin

Preclinical studies have demonstrated that gemcitabine acts as an effective inhibitor of DNA repair [23]. In fact, synergistic cytotoxicity was observed under conditions where gemcitabine inhibited adequate repair of DNA damage caused by cisplatin or radiation [24, 25]. While cisplatin alone has some activity in pancreatic cancer and induced a remission rate of 21% in one phase II study, median survival was not extended beyond 4.0 months [26]

Therefore, a phase II study was initiated to determine the impact of gemcitabine/cisplatin combination treatment on clinical efficacy and quality of life in pancreatic cancer patients [27]. A total of 41 patients received gemcitabine at a dose of 1,000 mg/m^2 (days 1, 8, and 15) and cisplatin at a dose of 50 mg/m^2 (days 1 and 15), every 29 days. In 35 evaluable patients, an overall RR of 11.5% (95% CI, 3.2–26.7%) was observed that was accompanied by disease stabilization ($\geq$ 3 months) in 57.1% of patients. In other words, this regimen achieved at least a transient stabilization of disease (CR + PR + SD) in 69% of patients. Median survival was 8.3 months and appears superior to the 3–5 months expected in patients receiving best supportive care alone. After 1 year, 28% of patients

Table 4. Survival of pancreatic cancer patients in relation to first-line treatment

Reference	15 5-FU/Cisplatin Phase III	8 Gemcitabine Phase III	7 Gemcitabine/5-FU Phase II	27 Gemcitabine/Cisplatin Phase II
n/eval	104/94	63/56	54/54	41/35
Regimen	5-FU 1,000 mg/m^2 CI 24 h, d 1–5, q d 29 Cisplatin 100 mg/m^2, d 1	Gemcitabine 1,000 mg/m^2 weekly × 7, 1 week rest then d 1, 8, 15, q d 29	Gemcitabine 1,000 mg/m^2 5-FU 600 mg/m^2 bolus d 1, 8, 15, q d 29	Gemcitabine 1,000 mg/m^2 d 1, 8, 15, q d 29 Cisplatin 50 mg/m^2, d 1, 15
Median survival, months	NA	5.7	7.0	8.3
6-month survival, %	38	46	61	69
9-month survival, %	NA	24	35	43
12-month survival, %	17	18	22	28

n/eval = Recruited/evaluable patients; CI = continuous infusion; 5-FU = 5-fluorouracil; NA = not available.

survived. Philip et al [28] used the identical regimen and achieved a median survival of 7.4 months (table 3). In a phase III randomized trial, Burris et al. [8] reported a 1-year survival of 2% in patients receiving 5-FU alone, and 18% with single-agent gemcitabine. In another randomized trial [15], 5-FU single-agent treatment induced a 1-year survival of 9%, while the combined application of 5-FU and cisplatin yielded a survival rate of 17% (table 4).

Combined treatment with gemcitabine and cisplatin appears to override the notorious chemoresistance of pancreatic cancer, although phase III trials are clearly necessary to determine if this regimen represents a marked progress of chemotherapeutic efficacy in this rather dismal patient entity. It remains unclear, however, the extent to which patient selection contributed to treatment outcome and the extent to which greater efficacy is achieved at the expense of quality of life. To answer these questions, randomized studies were initiated comparing single-agent gemcitabine to gemcitabine/cisplatin. In one such study by Colucci et al. [29], preliminary results have already been published. Thirty patients receiving a weekly application of gemcitabine 1,000 mg/m^2 achieved a response rate of 10%, while the other 32 patients treated with the same regimen of gemcitabine and cisplatin at a dose of 25 mg/m^2 reached a response rate of 42%. Clinical benefit responses were 45 and 38%, respectively. Although promising, the significance of these data is too premature to assess; moreover, survival data are not yet available.

A German multicenter study comparing gemcitabine 1,000 mg/m^2 (day 1, 8, and 15) to cisplatin 50 mg/m^2 plus gemcitabine 1,000 mg/m^2 (days 1 and 15), every 28 days, is currently ongoing.

Combination Therapy with Gemcitabine and 5-Fluorouracil

5-Fluorouracil (5-FU) has been thoroughly investigated as a combination partner for gemcitabine, and a number of preclinical studies demonstrate synergistic interactions between the two antimetabolites [27]. While gemcitabine increases 5-FU activity by depletion of cellular deoxyuridine monophosphate (dUMP) pools and inhibition of thymidylate synthase, 5-FU prevents inactivation of gemcitabine monophosphate by deamination.

Five phase I–II studies [7, 30–33] using gemcitabine in combination with standard doses of 5-FU yielded response rates (CR + PR) of 3.7–43% with a median survival of 7.0–13 months (table 5). One-year survival was reported in one study [7] and amounted to 22%. Among studies, however, there was not only a great variability of evaluable patient numbers, but also considerable variation among 5-FU applications, which included bolus, 3-hour, and continuous infusion regimens. It may, therefore, not be surprising to find marked differences among these studies in treatment response and survival.

A further four studies [34–37] evaluated high-dose 5-FU in various combinations with gemcitabine (table 6). They achieved response rates of 9.5–19%, and a median survival of 5.5–8.0 months. A comparison of survival achieved by gemcitabine in combination with standard-dose (7–13 months) or high-dose 5-FU (5.5–8 months) still does not provide evidence for a greater activity of either regimen (table 4). Clinical benefit response across all nine studies ranged from 45 to 57%.

Table 5. Gemcitabine plus standard-dose 5-FU

Reference	Phase	n/eval	Regimen	OR, %	SD, %	Clinical benefit, %	Survival months
7	II	54	5-FU 600 mg/m^2, bolus Gemcitabine 1,000 mg/m^2 d 1, 8, 15, q d 29	3.7	63	51	7.0
32	II	24/22	5-FU 600 mg/m^2, bolus Gemcitabine 1,000 mg/m^2 d 1, 8, 15, q d 29	12.5	22.4	(69.9*)	7.5
30	II	14	5-FU 500 mg/m^2, 3 h Gemcitabine 1,000 mg/m^2 d 1, 8, 15, q d 29	42.8	NA	50	13.0
31	I–II	26	5-FU 200 mg/m^2, CI, d 1–29 Gemcitabine 700–1,000 mg/m^2** d 1, 8, 15, q d 29	19.2	42	45	10.3
33	II	15	5-FU 200 mg/m^2, CI, d 1–21 Gemcitabine 600 mg/m^2 d 1, 8, 15, q d 29	13	40	NA	8.0

* Reported as PS improvement.

** Recommended gemcitabine dose = 900 mg/m^2.

n/eval = recruited/evaluable patients; 5-FU = 5-fluorouracil; CI = continuous infusion; OR = overall remission; SD = stable disease; NA = not available.

Table 6. Gemcitabine plus high-dose 5-FU

Reference	Phase	n/eval	Regimen	OR, %	SD, %	Clinical benefit, %	Survival months
37	I–II	23/21	5-FU 3,000 mg/m^2, CI 48h, weekly Gemcitabine 800–1,400 mg/m^2 weekly × 3, q d 29	19.0	33	57	5.5
35	II	63/48	FA 400 mg/m^2, 2 h, d 1 5-FU 400 mg/m^2 bolus, d 1 5-FU 2,000–3,000 mg/m^2, CI 48 h, d 1–2 Gemcitabine 1,000–1,500 mg/m^2, d 3 q 2 weeks	19.1	NA	50	8.0
34	I–II	22/21	Gemcitabine 1,000 mg/m^2, d 1 FA 250 mg/m^2, 2 h, d 1 5-FU 1,400–2,600 mg/m^2, CI 24 h, d 1 weekly × 3, q d 29	9.5	52	56	NA
36	II	15	Gemcitabine 1,000 mg/m^2, 5-FU 2,000 mg/m^2, CI 24 h weekly × 3, q d 29	14	50	NA	1-year survival = 36%

n/eval = Recruited/evaluable patients; FA = folinic acid; 5-FU = 5-fluorouracil; CI = continuous infusion; OR = overall remission; NA = not available.

Gemcitabine-Based Four-Drug Regimens

Reni et al. [38] performed a four-drug study including gemcitabine (600 mg/m^2 days 1 and 8), cisplatin (40 mg/m^2 day 1), epirubicin (40 mg/m^2 day 1) and continuous infusion 5-FU (200 mg/m^2 days 1–28). In 43 evaluable stage IV patients, a response rate of 58%, and a median survival of 9.4+ months (1-year survival = 40+%) were reported (table 3). Hematologic toxicity was reported with WHO grade 3–4 neutropenia in 51% and thrombocytopenia in 28% of patients. The results of this four-drug regimen are highly encouraging and may lead the way to intensive multi-drug regimens applicable in selected patients.

An additional trial [39] analyzed combined treatment with leucovorin (400 mg/m^2, day 1), 5-FU bolus (400 mg/m^2, day 1), 5-FU 48-hour continuous infusion (2,000–2,400 mg/m^2, days 1 and 2), followed by gemcitabine (800 mg/m^2, day 3) and oxaliplatin (85 mg/m^2, day 3). In 23 patients with advanced pancreatic cancer (n = 14) and cancer of unknown primary (n = 9), a response rate of 35% was observed. In the group of pancreatic cancer patients, 2 CRs, 2 PRs, a median progression-free survival of 8 months, and a median survival of 9 months were reported.

Gemcitabine Combined with Irinotecan or Docetaxel: Preliminary Data

Results of preliminary studies evaluating the clinical impact of irinotecan (CPT-11) or docetaxel in combination with gemcitabine in patients with pancreatic cancer have recently been reported.

Two phase II, multicenter studies of irinotecan, a topoisomerase inhibitor, plus gemcitabine in chemonaive patients with locally advanced and metastatic pancreatic cancer have demonstrated response rates of 20% (45 evaluable patients) and 15% (20 evaluable patients), respectively [40, 41]. Both studies used the same 3-week schedule, but the former administered irinotecan 100 mg/m^2 and gemcitabine 1,000 mg/m^2 on both days 1 and 8, while the latter administered a higher dose of irinotecan, 300 mg/m^2, on day 8 only with gemcitabine 900 mg/m^2 on days 1 and 8. Both regimens were considered well tolerated and relatively active with possibilities for further phase III study.

Based on promising phase II data [40], Rocha Lima and colleagues have initiated a randomized multicenter phase III trial (MUSC 8982) comparing the combination of irinotecan 100 mg/m^2 (days 1 and 8), plus gemcitabine 1,000 mg/m^2 (days 1 and 8), every 21 days; with gemcitabine 1,000 mg/m^2 (weekly × 7 for the 1st cycle, then days 1, 8, and 15), every 28 days. The primary endpoint is survival, with secondary measures of objective response, CA19-9, time to treatment failure, safety, PS, weight loss, albumin, and quality of life. Target accrual is 350 patients (175 per study arm) at a rate of 20 per month; follow-up will be 12 months. The investigators have accrued 60 patients, and seek a 2-month difference in median survival (Rocha Lima, personal communication).

In a phase I study, maximum tolerated dose study of escalating dose levels of docetaxel (25–40 mg/m^2) and gemcitabine (800 or 1,000 mg/m^2) in 25 chemonaive patients with locally advanced or metastatic pancreatic carcinoma, the recommended dose level was established at gemcitabine 1,000 mg/m^2 plus docetaxel 35 mg/m^2 administered weekly at 3-week intervals [42]. Dose-limiting toxicities included WHO grades 3 and 4 gastrointestinal toxicity and leukopenia. Preliminary efficacy results in the phase II ongoing study are encouraging with a 23% objective response rate and disease stabilization rate of 69% in 13 patients included thus far.

A phase I/II study in pancreatic cancer evaluated two regimens of gemcitabine and docetaxel: gemcitabine 800 mg/m^2 on days 1, 8 and 15 and docetaxel 75 mg/m^2 on day 1 of a 28-day schedule (Group A, n = 18), and gemcitabine 1,000 mg/m^2 and docetaxel 40 mg/m^2 on days 1 and 8 on a 21-day schedule (Group B, n = 11) [43]. The former schedule (A) was changed due to excessive hematologic toxicity requiring a dose reduction in 13 patients. (Schedule B, days 1 and 8 every 21 days, is the recommended regimen [Jacobs, pers. commun.]) Of the 25 patients evaluable for response, 7 (28%) achieved a PR and 10 (40%) either a minor response or stable disease. Sites of response were pancreas, peritoneum, lung, skin, and liver. Median time to progression was 5.25 months. The regimen in Group B was better tolerated with only two patients with hematologic toxicity (grade 2) versus 13 patients (grades 2/3) in Group A. The authors concluded that the response and survival data were encouraging given the poor prognosis for this cancer and the few palliative choices available.

In another phase II study in which all patients had metastatic disease, gemcitabine 600 mg/m^2 on days 1, 8, and 15 plus docetaxel 60 mg/m^2 on day 1 over 28-day cycles yielded an overall response rate of 8% (2/24 patients) including one CR [44]. However, an additional 4 of 7 patients with SD after four cycles had a greater than 75% reduction in CA 19-9 titer.

Table 7. Ongoing gemcitabine studies in pancreatic cancer

Study	Design	Chemotherapy	Investigator
MUSC 8982	Randomized Phase III	Gem + CPT-11 vs. gem	Rocha Lima
CALGB 89805	Phase II	Gem + radiation	Blackstock/Tempero
CALGB 89904	Randomized Phase II	Gem + cis; gem + doc; gem + CPT-11; high-dose single-agent gem	Kulke, Tempero
ECOG E-1298	Phase II	Gem + doc	Shepard
NCCTG 964352	Phase I	Gem + cis + radiation	Not available

CALGB = Cancer and Leukemia Group B; cis = cisplatin; CPT-11 = irinotecan; doc = docetaxel; ECOG = Eastern Cooperative Oncology Group; gem = gemcitabine; MUSC = Medical University of South Carolina; NCCTG = North Central Cancer Treatment Group.

Gemcitabine and Matrix Metalloprotease Inhibitors

Matrix metalloproteases (MMPs) represent a group of zinc-dependent enzymes involved in remodelling and turnover of extracellular matrix proteins, play a role in wound healing, and are involved in the pathogenesis of arthritis. Because MMPs are related to the tumor's ability to metastasize and the in the process of angiogenesis, high expression of MMPs is associated with cancer malignancy. Treatment with MMP inhibitors (MMPIs) alone or in combination with cytotoxic therapy is a novel approach in the control of tumor progression and, thus, the management of malignancies. Based on promising preclinical studies, synthetic MMPIs, such as marimastat, BAY 129566, CGS-27023A, prinomastat (AG-3340), BMS-275291, and metastat (COL-3), have been developed and included in clinical trials [45]. These drugs are involved at all stages of clinical drug development. The MMPIs have been evaluated as single agents, as well as in combination with other chemotherapeutic agents with the objective of reducing the size and number of metastatic lesions.

To determine whether MMPIs are capable of potentiating the effects of chemotherapy, various phase I trials were initiated to examine the safety of concomitant treatment. In a phase I study of the combination of gemcitabine and marimastat as first-line therapy [46], sequential marimastat doses of 5, 10, 15, and 20 mg BID were evaluated in 31 patients. Gemcitabine was administered at a dose of 1,000 mg/m^2 weekly for 3 of 4 weeks. Six patients experienced significant musculoskeletal toxicity related to marimastat therapy. Other toxicities included grade 4 elevated bilirubin, myelopsuppression, abnormal liver function tests, and back pain; the remaining toxicities were mild. Of the 11 evaluable patients, response was detected in 2 patients and stable disease in 6 patients. Sustained declines in CA19-9 were recorded in 9 patients. The authors concluded that marimastat, when combined with gemcitabine, did not appear to increase the incidence or severity of chemotherapy-related adverse events.

A number of phase III clinical trials comparing gemcitabine to MMPIs are ongoing, but only one, conducted by Rosemurgy et al., has been reported thus far [47, 48]. This study compared gemcitabine to marimastat as first-line therapy in 414 patients with unresectable pancreatic cancer. Patients were randomized to marimastat (5, 10, or 25 mg BID) or gemcitabine 1,000 mg/m^2 weekly for 7 of 8 weeks and then weekly for 3 of 4 weeks until the occurrence of disease progression or toxicity. With the study designed to detect a 16% or greater reduction in mortality, no statistically significant differences between gemcitabine and the three doses of marimastat were found in terms of the primary endpoint of overall survival. Safety data revealed no marked differences between the treatment groups other than the expected side effects of musculoskeletal toxicity with marimastat and the hematologic toxicity with gemcitabine.

Future Directions

A number of ongoing studies in advanced metastatic and/or locally advanced pancreatic cancer utilizing gemcitabine in combination with other agents is summarized in table 7.

Conclusions

Gemcitabine has been successfully introduced as a well-tolerated agent in the treatment of pancreatic cancer, and is presently recommended as the standard of care for first-line treatment of pancreatic cancer. The activity observed with the combination of gemcitabine with cisplatin or 5-FU appears promising (table 6), although its superiority to single-agent treatment regarding response rates and survival needs to be confirmed in randomized, phase III trials, which are ongoing or completed but not yet published. Randomized trials comparing single-agent gemcitabine to combination treatment are presently ongoing. Gemcitabine-based four-drug regimens promise a further increase of efficacy, but confirmatory trials are needed. Preliminary data from the recent coupling of gemcitabine with irinotecan, docetaxel, or MMPIs offer another encouraging alternative for pancreatic cancer.

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