Improvements in Survival and Clinical Benefit With Gemcitabine as First-Line Therapy for Patients With Advanced Pancreas Cancer: A Randomized Trial

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Purpose: **Most patients with advanced pancreas cancer experience pain and must limit their daily activities because of tumor-related symptoms. To date, no treatment has had a significant impact on the disease. In early studies with gemcitabine, patients with pancreas cancer experienced an improvement in disease-related symptoms. Based on those findings, a definitive trial was performed to assess the effectiveness of gemcitabine in patients with newly diagnosed advanced pancreas cancer.**

Patients and Methods: **One hundred twenty-six patients with advanced symptomatic pancreas cancer completed a lead-in period to characterize and stabilize pain and were randomized to receive either gemcitabine 1,000 mg/m^2 weekly × 7 followed by 1 week of rest, then weekly × 3 every 4 weeks thereafter (63 patients), or to fluorouracil (5-FU) 600 mg/m^2 once weekly (63 patients). The primary efficacy measure was clinical benefit response, which was a composite of measurements of pain (analgesic consumption and pain intensity), Karnofsky performance status, and weight. Clinical benefit required a sustained (≥ 4 weeks) improvement in at least one parameter without worsening in any others. Other measures of efficacy included response rate, time to progressive disease, and survival.**

Results: **Clinical benefit response was experienced by 23.8% of gemcitabine-treated patients compared with 4.8% of 5-FU–treated patients (P = .0022). The median survival durations were 5.65 and 4.41 months for gemcitabine-treated and 5-FU–treated patients, respectively (P = .0025). The survival rate at 12 months was 18% for gemcitabine patients and 2% for 5-FU patients. Treatment was well tolerated.**

Conclusion: **This study demonstrates that gemcitabine is more effective than 5-FU in alleviation of some disease-related symptoms in patients with advanced, symptomatic pancreas cancer. Gemcitabine also confers a modest survival advantage over treatment with 5-FU.**

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ADVANCED-STAGE, surgically unresectable pancreas cancer is an aggressive and lethal disease. Less than 10% of patients survive for a year after diagnosis, and many suffer from increasingly severe pain, nausea and vomiting, anorexia, weight loss, and weakness as the disease progresses.[1-7] Diagnosis usually occurs too late to attempt a cure with surgery or radiotherapy. Systemic treatment is used for patients with widespread disease, but the impact of existing chemotherapy is negligible. Fluorouracil (5-FU) has been studied most extensively using a variety of doses and schedules, but the response rate rarely exceeds 20%, and no consistent effect on disease-related symptoms or survival has been demonstrated.[7-10] Other single agents or combinations of drugs offer little improvement over single-agent 5-FU. In fact, most combination regimens just induce more toxicities for the patient.[7,8,11-18]

Gemcitabine (difluorodeoxycytidine; dFdC) is a novel nucleoside analog that has a broad spectrum of antitumor activity in preclinical murine leukemia and solid tumor models.[19] The drug requires intracellular phosphorylation that results in the accumulation of difluorodeoxycytidine triphosphate (dFdCTP).[20] The dFdCTP competes with deoxycytidine triphosphate (dCTP) for incorporation into DNA, which in turn inhibits DNA synthesis.[20,21] In addition, the drug reduces intracellular deoxynucleoside triphosphate pools, presumably by inhibiting ribonucleotide reductase.[22] In a previous phase II trial, gemcitabine was administered at doses of 800 to 1,250 mg/m^2 per week to 44 patients with advanced pancreas cancer.[23] A partial response rate of 11% was observed. The median duration of response was 13 months, with 23% of patients still alive at 1 year.[23] Improvements in disease-related symptoms were reported both by responding patients and by

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a number of patients who had stable disease. These improvements, which were greater than expected from the objective tumor response rate, took the form of decreased pain severity and decreased requirement for opioid analgesics, increased appetite and weight gain, and improved functional status. These improvements lasted for up to 10 months. The improvement in pain, performance status, and weight in some of the patients receiving gemcitabine was encouraging.

The concept of a chemotherapy-induced, palliative effect on disease-related symptoms in patients with pancreas cancer has been only relatively recently addressed in the literature. Cullinan et al[24] began to explore this concept in 1985 when they tried to quantify whether treatment with various 5-FU–containing regimens resulted in an improvement in performance status, a weight gain, or an improvement in tumor-related symptoms in patients with gastric or pancreas cancer. Their work and the work of O'Connell[25] and Buroker et al[26] indicated these parameters could be assessed as measures of clinical improvement with a particular therapy. Based on that prior work and a desire to quantitate any improvement in disease-related symptoms, we have developed the concept of clinical benefit as a method to assess the effect of chemotherapy. We have prospectively defined clinical benefit as a composite assessment of pain, performance status, and weight.[27] A patient is categorized as a clinical benefit responder when there is a sustained improvement in these parameters. Clinical benefit is measured prospectively as a primary end point in the present study. An assessment of quality of life was not used because, at the time of the design of this study, no quality-of-life instrument had been prospectively validated in patients with advanced, symptomatic pancreas cancer. However, the concept of a clinical benefit responder has also not been prospectively validated.

Because gemcitabine appeared to have some antitumor effect and possibly an even greater impact on the parameters of clinical benefit for patients with pancreas cancer, a randomized trial of gemcitabine versus the standard agent 5-FU was performed in patients with advanced pancreas cancer. This trial was performed to determine if gemcitabine provided any advantage (in terms of clinical benefit, objective response [complete or partial response], time to progressive disease, or survival) over treatment with single-agent 5-FU. Single-agent 5-FU was chosen as the control because it is both easily administered and well tolerated, and no other agent or combination of agents has proven superior to 5-FU for treatment of patients with advanced pancreas cancer.[7-22] Use of a placebo as a control was not deemed acceptable by the majority of the participating investigators who designed this study. Single-agent 5-FU was used on a schedule to match that of gemcitabine at a dose judged prospectively to be equitoxic to gemcitabine and was deemed an acceptable control arm by the investigators designing the study.

PATIENTS AND METHODS

Patient Population

This randomized study included patients with a pathologic diagnosis of pancreas cancer that was locally advanced or metastatic and not amenable to curative surgical resection. Patients who had received previous chemotherapy were not eligible. Patients who had received prior irradiation could be included if the irradiated area was not the only source of measurable or assessable disease. Patients were required to have a baseline Karnofsky performance status of at least 50 and an estimated life expectancy of at least 12 weeks. An adequate baseline bone marrow reserve was necessary and defined as WBC count $\geq$ 3,500/μL, platelet count $\geq$ 100,000/μL, and hemoglobin level $\geq$ 9.5 gm/dL. Adequate baseline hepatic function (defined as a total bilirubin level $\leq$ 2.0 mg/dL, AST and ALT $\leq$ three times the upper limits of normal, unless the tumor involved the liver, in which case the transaminase levels could be up to five times the upper limits of normal) and adequate renal function (defined as serum creatinine concentration $\leq$ 1.5 mg/dL) were also required.

The primary end point of the trial was to measure improvement in specific disease-related signs and symptoms (clinical benefit). Therefore, patients were eligible only if one or more of the following conditions held: (1) baseline Karnofsky performance status of less than 80; (2) baseline analgesic consumption of $\geq$ 10 morphine-equivalent mg/d; and (3) baseline pain intensity score of $\geq$ 20 mm (of a possible 100 mm on the Memorial Pain Assessment Card [MPAC]).[28]

Patient Assignment

Signed and witnessed informed consent was obtained from each patient before entry onto the study. For 2 to 7 days before treatment started, all patients underwent a pain stabilization period. Analgesics were adjusted so that patients received morphine sulfate or hydromorphone in a fixed regimen that aimed to provide adequate pain control with no more than four supplemental doses of analgesics per day to control breakthrough pain. If patients did not tolerate these analgesics or their pain could not be stabilized, they did not proceed to the treatment part of the study. Randomization of patients with stabilized pain to treatment with either gemcitabine or 5-FU occurred immediately before starting study drug treatment and was performed at a central location. Treatment was single blind. The study drug was not blinded to the investigator, because a rash was a potential side effect of treatment with both 5-FU and gemcitabine. A rash secondary to 5-FU would indicate that a dosage adjustment with the drug could be needed (because of that toxicity), whereas a rash secondary to gemcitabine would not require a dose reduction. Although the treating physician knew whether the patient was receiving gemcitabine or 5-FU, treatment allocation was not known by the patients, who filled out their MPAC card as well as an analgesic consumption diary. In addition, performance status was assessed by two independent observers.

Treatment

Gemcitabine hydrochloride (Gemzar; Eli Lilly and Company, Indianapolis, IN) was supplied as a lyophilized powder. The drug was

diluted in normal saline and administered intravenously over 30 minutes by an infusion pump. For the first cycle, patients received gemcitabine 1,000 mg/m^2 once weekly for up to 7 weeks (the first cycle was terminated early if ≥ grade 2 nonhematologic or ≥ grade 3 hematologic toxicity occurred), followed by a week of rest. Thereafter, gemcitabine was administered once weekly for 3 consecutive weeks out of every 4 weeks. Patients experiencing toxicity of World Health Organization (WHO) grade 2 or less had subsequent gemcitabine doses escalated by 25% up to, but not exceeding, a dose of 1,250 mg/m^2.

5-FU was supplied as an aqueous solution. It was diluted with up to an additional 50 mL of normal saline or a solution of 5% dextrose and water and administered intravenously over 30 minutes. 5-FU 600 mg/m^2 was administered once weekly, with a cycle defined as one 4-week period. Doses were adjusted or omitted for toxicity according to a defined schedule. Dose escalation of 5-FU was allowed but not implemented in any patient. Treatment with gemcitabine or 5-FU continued until there was evidence of disease progression or until there was significant clinical deterioration because of tumor-related symptoms. Patients were not allowed to receive concomitant radiation therapy, chemotherapy, hormonal therapy, or corticosteroids during the trial.

Efficacy and Safety Evaluation

Clinical benefit. The principal efficacy end point used in this study was clinical benefit as derived from measurement of three common debilitating signs or symptoms present in most patients with advanced pancreas cancer, including pain, functional impairment, and weight loss. Pain (assessed by pain intensity and analgesic consumption) and functional impairment (assessed by Karnofsky performance status) comprised the primary measures of clinical benefit. Weight change (assessed by body weight) was considered a secondary measure. Patients participated in a pain stabilization lead-in period to establish base-line measures, then pain intensity was recorded daily (by the patients filling out both an MPAC card and an analgesic consumption diary). The other parameters were assessed weekly. Karnofsky performance status was assessed by two independent observers. Disease status for patients on both arms of the study was assessed every 4 weeks.

Each patient was classified as either positive, stable, or negative for each of the primary clinical benefit measures (pain or performance status) (Table 1). The designation for pain integrated both the subjective report of pain intensity as well as analgesic consumption. In all cases, positive indicated a sustained (≥ 4 weeks) improvement over baseline (Table 1). If the patient was stable on both primary measures of clinical benefit (pain and performance status), the patient was then classified as either positive or nonpositive on the basis of the secondary clinical benefit measure of weight (Table 1).

For patients to achieve an overall rating of positive clinical benefit response, they had to be positive for at least one parameter (pain, performance status, or weight) without being negative for any of the others (Fig 1). This improvement had to last for at least 4 weeks. The primary measures of pain and performance status were evaluated first; a patient who was only stable on these primary measures could be classified as having achieved an overall clinical benefit response only if weight was positive. All other patients were classified as not having achieved clinical benefit response.

Other measures of efficacy. In addition to the clinical benefit measurement, objective tumor response, survival, and time to progressive disease were assessed prospectively as additional end points

Table 1. Classifications for Clinical Benefit Measures

Primary measures
Pain
Pain intensity (measured daily on the MPAC 0-100 visual analog scale)
Positive: An improvement of ≥ 50% from baseline sustained for ≥ 4 weeks, assuming a minimum pain score ≥ 20
Negative: Any worsening from baseline, sustained for 4 weeks
Stable: Any other result
Analgesic consumption (measured weekly in morphine-equivalent milligrams)
Positive: A decrease of ≥ 50% from baseline, sustained for ≥ 4 weeks, assuming a minimum analgesic consumption ≥ 10
Negative: Any worsening from baseline, sustained for 4 weeks
Stable: Any other result
Karnofsky performance status (measured weekly)
Positive: An improvement of ≥ 20 points from baseline, sustained for ≥ 4 weeks, for patients with a performance status of 50, 60 or 70
Negative: Any worsening of ≥ 20 points from baseline, sustained for ≥ 4 weeks
Stable: Any other result
Secondary measure (measured weekly)
Weight
Positive: A weight gain (excluding third-space fluid) of ≥ 7% from baseline, sustained for ≥ 4 weeks
Nonpositive: Any other result

of the trial. A complete tumor response was defined as disappearance of all clinical evidence of tumor for a minimum of 4 weeks, during which time the patient was free of all symptoms related to cancer. Partial response was defined as ≥ 50% decrease in the sum of the products of 2 perpendicular diameters of all measurable lesions for a minimum of 4 weeks. During this time, there must have been no increase of ≥ 25% in the size of any single lesion or the appearance of any new lesion. Progressive disease was defined as an increase in the sum of the products of the diameters of measurable lesions by ≥ 25%, the appearance of any new lesion, or a deterioration in clinical status that was consistent with disease progression. Patients who failed to meet the criteria of complete response, partial response, or progressive disease, and who remained on study for at least 8 weeks, were classified as having stable disease. Time to progressive disease was defined as the time between administration of the first dose of study drug and the time the patient was classified as having progressive disease or discontinued therapy, whichever happened earlier.

Safety. Patients were evaluated by weekly history and physical examinations, complete blood counts, chemistry profiles, and urinalyses. All signs, symptoms, or laboratory abnormalities were assessed using WHO criteria for toxicities.[29]

RESULTS

One hundred sixty patients entered this trial through 17 sites in Canada and the United States between July 1992 and March 1994. Thirty-four patients did not proceed beyond the pain stabilization period (lead-in period) and were not randomized. These 34 patients included 17 patients who were no longer eligible (11 with liver function deterioration beyond eligibility criteria, two with de-

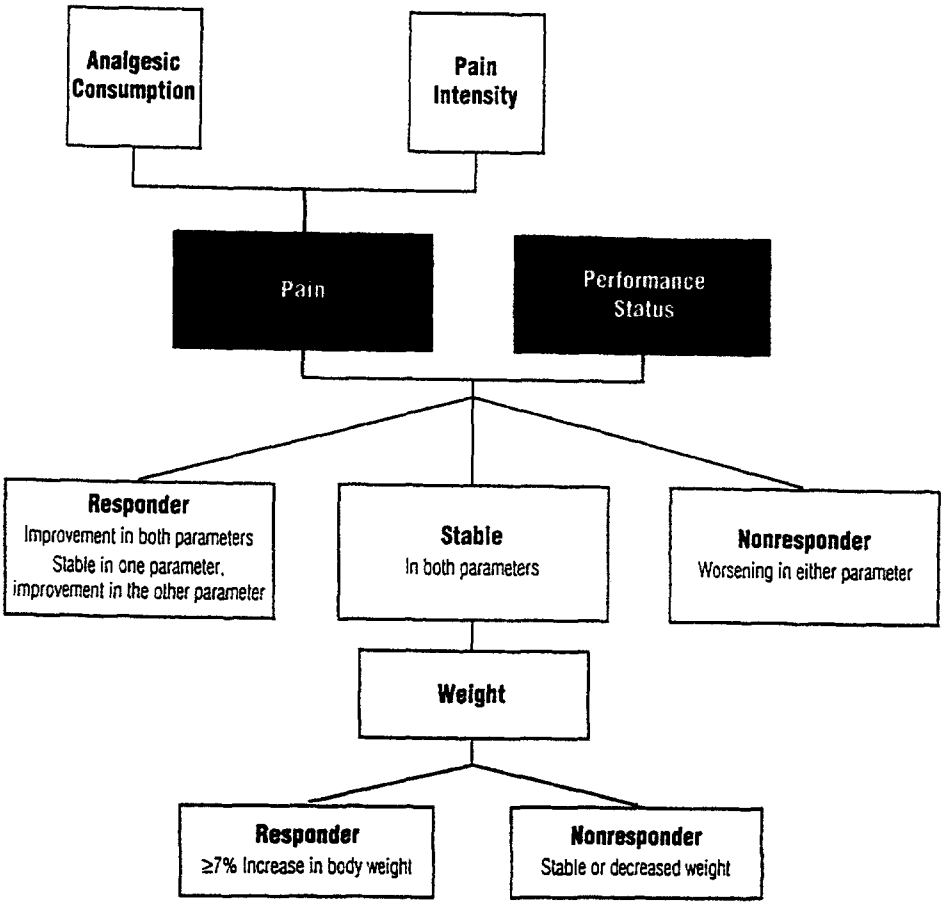

Fig 1. Flow diagram for assessment of clinical benefit.

creases in hemoglobin, two with incorrect pathology, one with elevated creatinine, and one with ascites), 10 patients in whom pain control could not be achieved, four patients who developed other medical problems precluding their entry onto the study, and three patients who decided not to proceed with further evaluation.

Of the 126 patients who were randomized to treatment, 63 received gemcitabine and 63 received 5-FU (Table 2). The two groups were well balanced for prognostic factors. Most patients had pain at entry; 43 (68%) on gemcitabine and 39 (62%) on 5-FU had a baseline pain intensity score greater than 20 points. Sixty patients (95%) in each group required more than 10 morphine-equivalent mg/d for control of pain. Similarly, most patients had an impaired performance status at entry. A Karnofsky performance status of 50 to 70 was recorded in 44 (70%) and 43 (68%) patients randomized to gemcitabine and 5-FU treatment, respectively.

Clinical Benefit

Fifteen (23.8%) gemcitabine patients and three (4.8%) 5-FU patients were classified as positive in the pain category (ie, pain intensity and/or analgesic use was reduced) and 25 (39.7%) gemcitabine patients and 38 (60.3%) 5-FU patients were classified as stable in this category (ie, both pain and analgesic use were stable) (Fig 2A). Both pain and Karnofsky performance status improved in four gemcitabine patients, and 11 other patients taking gemcitabine had an improvement in pain with no worsening of performance status (Fig 2B). Therefore, 15 (23.8%) gemcitabine patients were classified as clinical benefit responders by their primary measures. On the 5-FU arm, one patient had an improvement in performance status and stabilization of pain, and two patients had an improvement in pain with stabilization of performance status. An additional two patients who had an improved performance status and one with improved pain had negative scores by other parameters and, therefore, were not responders. Therefore, only three (4.8%) 5-FU patients experienced clinical benefit as assessed by their primary measures (pain and Karnofsky performance status). With regard to the secondary measure of clinical benefit, weight gain (Fig 2C), one patient in the gemcitabine arm and

Table 2. Characteristics of Patients Randomized to Treatment With Either Gemcitabine or 5-FU

Characteristic	Gemcitabine		5-FU	
	No.	%	No.	%
No. of Patients	63		63	
Sex				
Male	34	54	34	54
Female	29	46	29	46
Median age, years				
Range	62	37-79	61	36-77
Stage				
II	9	14	5	8
III	9	14	10	16
IV	45	72	48	76
Karnofsky performance status				
50-70	44	70	43	68
80-90	19	30	20	32
Baseline pain intensity score				
0-19	20	32	24	38
20-29	13	21	10	16
30-39	12	19	10	16
40-49	9	14	10	16
50-100	9	14	9	14
Baseline analgesic requirement (morphine-equivalent mg)				
0-49	19	30	17	27
50-100	21	33	19	30
≥ 100	23	37	27	43

none in the 5-FU arm had a positive weight change. However, the gemcitabine-treated patient had already been categorized as a clinical benefit responder by primary measures, and thus, the number of patients experiencing a clinical benefit response with gemcitabine treatment remained at 15 (23.8%). In summary, the clinical benefit response was 23.8% for gemcitabine and 4.8% for 5-FU. This was a highly statistically significant difference (P = .0022, using the two-sided test for difference in binomial proportions).

The median time to achieve a clinical benefit response was 7 weeks for the gemcitabine-treated patients (n = 15) and 3 weeks for the 5-FU-treated patients (n = 3). The mean duration of clinical benefit was 18 weeks and 13 weeks for gemcitabine-treated and 5-FU-treated patients, respectively.

Other Measures of Efficacy

At the data cutoff date, median survival was 5.65 months for gemcitabine patients and 4.41 months for 5-FU patients (Fig 3A). The probability of surviving beyond 12 months was 18% for gemcitabine compared with 2% for 5-FU. The survival advantage for gemcitabine was highly statistically significant (log-rank test, P = .0025).

Fifty patients (79.4%) discontinued 5-FU because of progressive disease, compared with 41 patients (65.1%) who received gemcitabine. The median time to progressive disease for gemcitabine was 9 weeks compared with 4 weeks for the 5-FU arm (log-rank test, P = .0002) (Fig 3B). Other reasons for discontinuation of assigned treatment included adverse events (nine gemcitabine patients whose reasons included ascites [n = 1], depression [n = 1], dyspnea [n = 1], abnormal electrocardiogram [n = 1], gastrointestinal hemorrhage [n = 2], maculopapular rash [n = 1], and nausea [n = 2]; and three 5-FU patients whose reasons included carcinoma [n = 1], jaundice [n = 1], and nausea [n = 1]; no significant differences between the two arms, P = .1264), death (two patients in each treatment group), lack of efficacy with stable disease (two patients each), clinical relapse (one patient each), satisfactory response (one patient each), and protocol interim criteria for continued treatment were not met in one 5-FU–treated patient. Six gemcitabine-treated patients and three 5-FU–treated patients chose to leave the study for personal reasons. It must be remembered that, because patients were on treatment for a longer period of time with gemcitabine (because of a lack of tumor progression) than they were with 5-FU, the opportunity for a patient to experience an adverse event (or a desire to discontinue therapy for personal reasons) was much greater for those patients on gemcitabine than for those on 5-FU.

Fifty-six gemcitabine patients had bidimensionally measurable disease at study entry. Three of these patients achieved a partial response for an overall tumor response rate of 5.4%. In addition, 22 patients (39%) had stable disease. Among 57 5-FU–treated patients with measurable disease, none (0%) achieved a complete or partial response. Eleven patients (19%) had stable disease. The difference in partial response rates was not statistically significant.

Kaplan-Meier curves were plotted to compare patients with a clinical benefit response from both arms of the study with patients who had no clinical benefit response. Although this analysis was not planned before the study, it was included to explore the interaction between clinical benefit and traditional end points used in cancer clinical trials. In that analysis, patients with a clinical benefit response had a longer median survival (10.7 *v* 4.8 months) and time to progressive disease (3.7 *v* 1.6 months) than patients who did not have a clinical benefit response.

Toxicity

Both drugs were generally well tolerated throughout the study (Tables 3 and 4). The incidence of hematologic toxicity was low. As listed in Table 3, WHO grade 4 neutropenia (granulocyte count < 500/μL) was reported

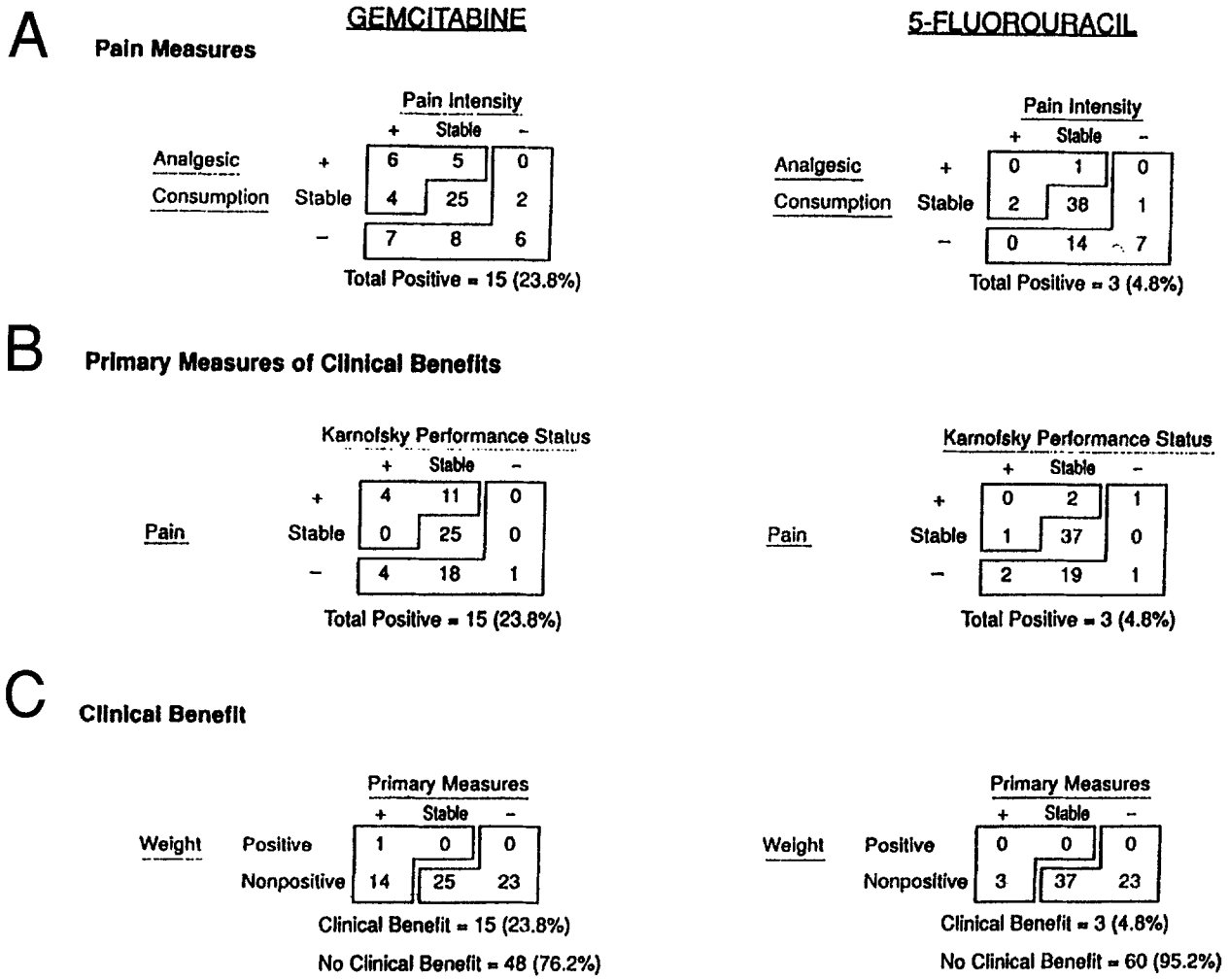

Fig 2. (A) Pain improvement classifications for gemcitabine and 5-FU. (B) Primary clinical benefit measures for gemcitabine and 5-FU. (C) Overall clinical benefit (including primary measures and weight) with gemcitabine and 5-FU.

in 6.9% of gemcitabine patients and 3.3% of 5-FU patients (not statistically significant by a normalized Z-score P value of .1841). Grade 3 and 4 neutropenia was noted in 25.9% of gemcitabine patients and 4.9% of 5-FU–treated patients ($P < .001$ by a normalized Z-score). However, there were no serious infections in either treatment group, and grade 4 thrombocytopenia was not observed in either group. The incidence of WHO grade 3 or 4 anemia was 9.7% with gemcitabine and 0% with 5-FU. The number of patients who required RBC transfusions for either tumor-related or drug-related toxicities was 17 with gemcitabine and five with 5-FU.

As listed Table 4, drug-related symptomatic toxicity was generally mild in both treatment groups. Grade 1 or 2 fevers were relatively common, occurring in 30.1% of gemcitabine patients and in 16.1% of 5-FU patients. Minor (grade 1 or 2) rashes were also commonly observed (gemcitabine 23.8% *v* 5-FU 12.9%). The incidence of grade 3 and 4 nausea/vomiting was 9.5% and 3.2% for gemcitabine compared with 4.8% and 0% for 5-FU. Hair loss was mild to moderate in all cases, and no patient experienced total alopecia.

Two patients on each arm died on treatment during the trial; all four deaths were secondary to complications of pancreas cancer.

DISCUSSION

Attempts to develop effective systemic therapies for patients with locally advanced or metastatic pancreas cancer have met with little success. 5-FU has been the most extensively studied single agent in this disease, with published objective response rates ranging from 0% to 60%.[30]

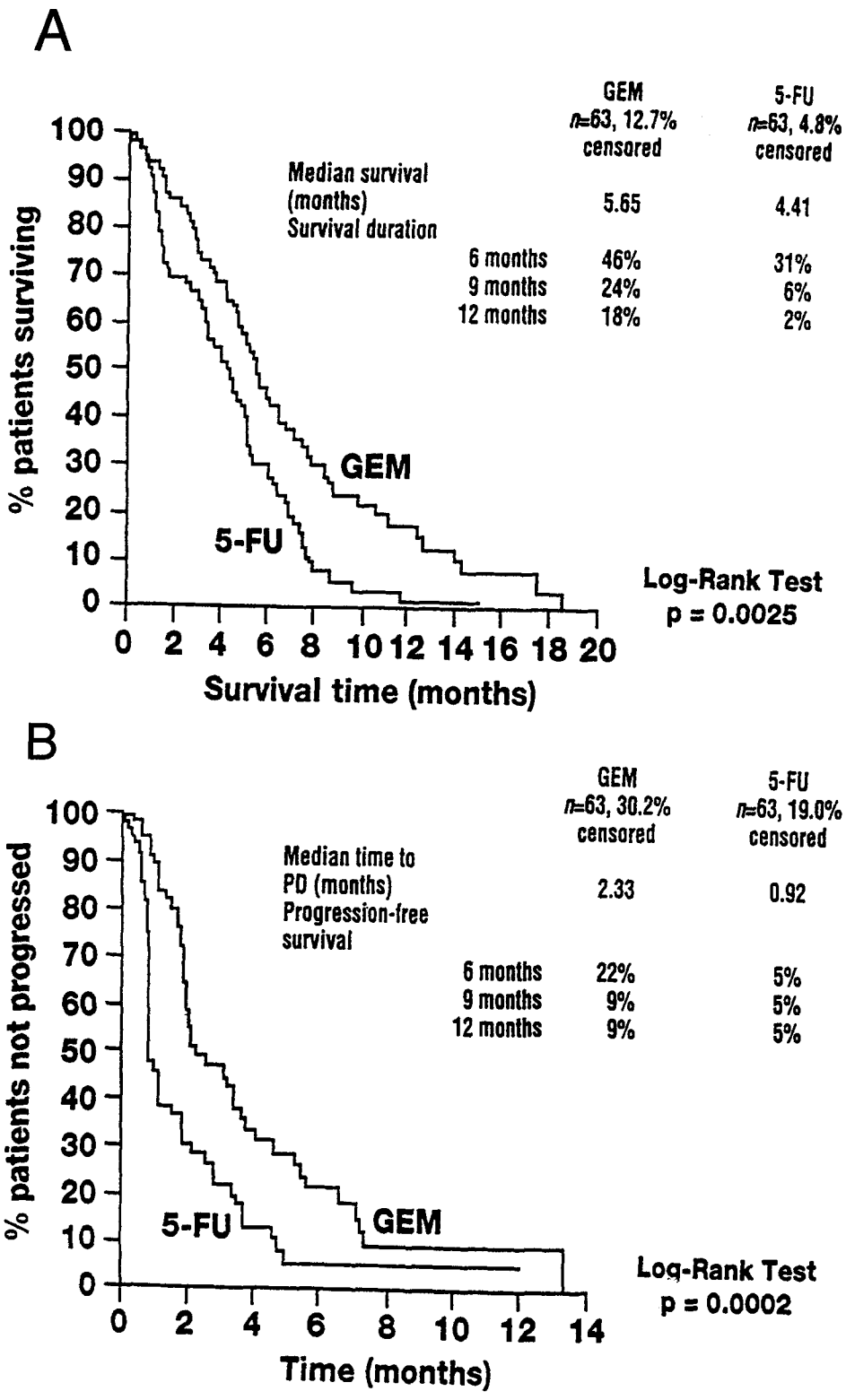

Fig 3. (A) Survival with treatment with gemcitabine and 5-FU. (B) Time to tumor progression during treatment with gemcitabine and 5-FU.

Table 3. Summary of Maximum WHO Grades for Laboratory Toxicity

	WHO Grade									
	0		1		2		3		4	
	GEM	5-FU	GEM	5-FU	GEM	5-FU	GEM	5-FU	GEM	5-FU
Segmented neutrophils	37.9	82.0	10.3	3.3	25.9	9.8	19.0	1.6	6.9	3.3
WBCs	29.0	85.5	25.8	6.5	35.5	6.5	9.7	1.6	0.0	0.0
Platelets	53.2	85.5	16.1	11.3	21.0	1.6	9.7	1.6	0.0	0.0
Hemoglobin	35.5	54.8	30.6	27.4	24.2	17.7	6.5	0.0	3.2	0.0
Bilirubin	83.6	74.6	3.3	6.3	9.8	9.5	1.6	6.3	1.6	3.2
Alkaline phosphatase	29.5	36.5	32.8	23.8	21.3	27.0	16.4	9.5	0.0	3.2
Aspartate transaminase	27.9	47.6	41.0	27.0	19.7	23.8	9.8	1.6	1.6	0.0
Alanine transaminase	27.9	61.9	32.8	23.8	29.5	14.3	8.2	0.0	1.6	0.0
Blood urea nitrogen	91.8	90.5	8.2	9.5	0.0	0.0	0.0	0.0	0.0	0.0
Creatinine	98.4	100.0	1.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0

NOTE. Values given are percentage of patients.
Abbreviation: GEM, gemcitabine.

On closer examination of these trials, the highest response rates occurred in the oldest studies, when objective responses were determined on the basis of decrease in hepatomegaly and change in the size of palpable lesions. Studies of single-agent 5-FU published since 1985 (since which time computed tomographic assessment of tumor response became standard), have reported response rates ranging from 0% to 19%.[6-8,31] Median survival time for patients treated with single-agent 5-FU have ranged from 4.2 to 5.5 months.[14,15,24]

The high initial response rates reported for several multiagent regimens, such as the Mallinson regimen (5-FU, methotrexate, vincristine, and cyclophosphamide induction followed by maintenance 5-FU and mitomycin),[32] the 5-FU, doxorubicin, and mitomycin (FAM) regimen,[33,34] the cisplatin, cytarabine, and caffeine (CAC) regimen,[30] and the streptozotocin, mitomycin, and 5-FU (SMF) regimen[36,37] appeared to herald advances in the treatment of patients with advanced pancreas cancer. Unfortunately, subsequent randomized phase III trials failed to confirm the high level of activity observed in the initial trials, and the newer regimens were found to confer no survival advantage over single-agent 5-FU.[13,14] Therefore, when the present study was designed, single-agent 5-FU

Table 4. Summary of Maximum WHO Grades for Symptomatic Toxicity

	WHO Grade									
	0		1		2		3		4	
	GEM	5-FU	GEM	5-FU	GEM	5-FU	GEM	5-FU	GEM	5-FU
Nausea/vomiting	36.5	41.9	28.6	25.8	22.2	27.4	9.5	4.8	3.2	0.0
Diarrhea	76.2	69.4	17.5	14.5	4.8	11.3	1.6	4.8	0.0	0.0
Constipation	90.5	88.7	4.8	4.8	1.6	4.8	3.2	1.6	0.0	0.0
State of consciousness	95.2	93.5	1.6	4.8	1.6	0.0	1.6	1.6	0.0	0.0
Pain	90.5	93.5	1.6	3.2	6.3	3.2	1.6	0.0	0.0	0.0
Fever	69.8	83.9	22.2	11.3	7.9	4.8	0.0	0.0	0.0	0.0
Cutaneous	76.2	87.1	17.5	8.1	6.3	4.8	0.0	0.0	0.0	0.0
Oral	85.7	85.5	11.1	12.9	3.2	1.6	0.0	0.0	0.0	0.0
Hemorrhage	100.0	98.4	0.0	0.0	0.0	1.6	0.0	0.0	0.0	0.0
Infection	92.1	96.8	4.8	1.6	3.2	0.0	0.0	0.0	0.0	0.0
Pulmonary	93.7	96.8	3.2	3.2	3.2	0.0	0.0	0.0	0.0	0.0
Hair	82.5	83.9	15.9	16.1	1.6	0.0	0.0	0.0	0.0	0.0
Peripheral neurotoxicity	98.4	98.4	1.6	1.6	0.0	0.0	0.0	0.0	0.0	0.0
Proteinuria	90.5	98.4	9.5	1.6	0.0	0.0	0.0	0.0	0.0	0.0
Cardiac rhythm	98.4	98.4	1.6	1.6	0.0	0.0	0.0	0.0	0.0	0.0
Allergic	100.0	98.4	0.0	1.6	0.0	0.0	0.0	0.0	0.0	0.0
Hematuria	87.3	100.0	12.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0

NOTE. Values given are percentage of patients.
Abbreviation: GEM, gemcitabine.

was selected as the control treatment. The dose of 5-FU (600 mg/m^2) was not the maximum possible for treatment of patients with pancreas cancer, but there is no evidence that either a higher dose of 5-FU or modulation with leucovorin would have been more effective.[11,12,17,38-41] In addition, an attempt was made in the trial design to select a dose of 5-FU that would be approximately equitoxic to the dose of gemcitabine. The weekly schedule of 5-FU was selected to allow the trial to be conducted on a single-blind basis.

A distinguishing feature of advanced-stage pancreas cancer is the high incidence of significant tumor-related symptoms.[2-5] Although a recent prospective study[6] indicated that pain in relatively early disease might not be as common as reported in retrospective studies of patients with cancer of the pancreas, it is still a substantial problem and becomes more compelling in the advanced stages. Nausea, vomiting, anorexia, a deterioration in performance status, and weight loss are also frequent characteristics of this disease.

The present trial was designed to determine how often gemcitabine controlled tumor-related symptoms and whether that control was better with gemcitabine than it was with 5-FU. The end point of clinical benefit response was created to provide a way in which the impact of therapy on tumor-related symptoms could be assessed in an unbiased, systematic, and objective fashion. Each of the clinical benefit components were validated measures (pain, performance status, and weight) and were believed to be particularly relevant outcomes in patients with pancreas cancer. The criteria established for positive change in these components, so a patient could be designated as having clinical benefit, were rigorous. Overall clinical benefit response required a sustained (at least 4 weeks) improvement in at least one component without a deterioration in any others. The criteria were defined in such a way that a positive change of this magnitude would be unexpected, given the natural history of advanced pancreas cancer, which is characterized by inexorable progression of symptoms and disability. It is important to point out that clinical benefit was not designed to be a quality-of-life instrument and that there has been no prospective evaluation of the clinical benefit parameters. However, at the time of the inception of this study, there was no disease-specific quality-of-life instrument available for patients with advanced pancreas cancer. Perhaps such a disease-specific quality-of-life instrument could have given us a way to measure both disease-related as well as drug-related symptoms. However, what was available from several investigators[24-26] was the fact that assessment of pain, performance status, and weight had been used to measure a chemotherapy-induced palliative effect on disease-related symptoms in patients with pancreatic and other gastrointestinal malignancies. The concept of clinical benefit was built on those foundations.

In this trial, gemcitabine was superior to 5-FU in terms of the primary end point: clinical benefit response. Clinically significant and sustained improvements in pain, analgesic consumption, and/or Karnofsky performance status were observed in 23.8% of gemcitabine patients compared with 4.8% of 5-FU patients (P = .0022). The onset of clinical benefit was relatively rapid (7 weeks for gemcitabine and 3 weeks for 5-FU). The duration of clinical benefit was 18 weeks for gemcitabine-treated patients and 13 weeks for those who received 5-FU. Because this study was conducted as a single-blinded study with only the patients blinded to the agent they were receiving, it is theoretically possible that in some way a patient or patients were able to find out what agent they were receiving. All efforts in conducting good clinical research were made to assure that this would not happen. In addition, the definitions for improvement in pain and analgesic consumption that defined clinical benefit were rigorous (both in terms of degree of change and duration of change). However, the single-blinded nature of the study should be remembered as one is interpreting the clinical benefit results of the study.

In this study of symptomatic patients, survival was a secondary end point and this, too, was superior with gemcitabine. There was a 5-week improvement in median survival duration for patients treated with gemcitabine compared with those who received 5-FU (5.65 v 4.41 months), and overall survival was significantly better for the gemcitabine-treated patients (P = .0025). Given the rapidly lethal nature of this disease, the 5-week extension translates into a 28% relative improvement in median survival. In addition, the 6-, 9-, and 12-month survival rates were higher with gemcitabine (46%, 24%, and 18%, respectively) than with 5-FU (31%, 6%, and 2%, respectively). Unfortunately, however, all patients had progressed within 14 months of starting therapy and there was no survival past 19 months.

In this trial, the beneficial effects of gemcitabine on tumor-related symptoms was not negated by frequent or severe treatment-related toxicities. Overall, both treatments were very well tolerated. Symptomatic toxicity from gemcitabine was mild, with a low incidence of nausea or vomiting and alopecia. Although grade 3 and 4 myelosuppression was slightly greater with gemcitabine than 5-FU, the incidence was very low compared to most cytotoxics and was rarely associated with clinically significant events.

Despite a modest tumor response rate of only 5.4% in the gemcitabine arm and 0% in the 5-FU arm, there was a statistically significant improvement in survival for patients who received gemcitabine. We believe these data indicate that, even with computed tomographic scans, the ability to detect changes in objective disease status in patients with pancreas cancer (which translates into improved survival) may be severely compromised by a local fibrotic response as well as by inflammation in the tumor bed. The data may also reflect the fact that in patients with advanced pancreas cancer, a less than 50% decrease in measurable tumor bulk or even objectively measured stable disease after treatment still may be associated with improved survival.

While additional improvement is clearly needed, these results are encouraging. In this trial, gemcitabine-treated patients had a significantly increased rate of clinical benefit compared with patients treated with 5-FU. This is also the first time in 30 years that a new agent has produced improved overall survival when compared directly with 5-FU. In addition, all therapy was given in the outpatient setting, and toxicity associated with gemcitabine was very modest. Future efforts will focus on integrating gemcitabine into multimodality treatment regimens and evaluating the drug in patients with earlier-stage disease.

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APPENDIX

Other Investigators and Their Institutions That Entered Patients on the Study Include·

Investigator	Institution
David S Alberts, MD	Arizona Cancer Center, Tucson, AZ
Thomas Brown, MD	Duke University Medical Center, Durham, NC
Frederick O Butler, MD	Methodist Hospital of Indiana, Inc, Indianapolis, IN
Richard Gralla, MD	Alton Ochsner Medical Foundation Hospital, New Orleans, LA
Daniel Haller, MD	University of Pennsylvania Medical Group, Philadelphia, PA
David Kelsen, MD	Memorial Sloan-Kettering Cancer Center, New York, NY
Walter Kocha, MD	London Regional Cancer Center, London, United Kingdom
Martin Oken, MD	Abbott Northwestern Hospital, Minneapolis, MN
Richard Schilsky, MD	University of Chicago, Chicago, IL
Amil Shah, MD	British Columbia Cancer Agency, Vancouver, Canada
Jamey Skillings, MD	Cancer Treatment & Research Foundation of Nova Scotia, Nova Scotia, Canada
James Willson, MD	University Hospitals of Cleveland, Cleveland, OH
Robert Wolf, MD	Duke University Medical Center, Durham, NC

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