An Investigational New Drug Treatment Program for Patients with Gemcitabine

Results for Over 3000 Patients with Pancreatic Carcinoma

Anna Maria Storniolo, M.D.[1]
Nathan H. Enas, M.S.[1]
Cheryl A. Brown, R.Ph.[1]
Maurizio Voi, M.D.[1]
Mace L. Rothenberg, M.D.[2]
Richard Schilsky, M.D.[3]

[1] Lilly Research Laboratories, Indianapolis, Indiana.

[2] Vanderbilt University Medical Center, Nashville, Tennessee.

[3] University of Chicago Cancer Research Center, Chicago, Illinois.

Supported by a grant from Eli Lilly and Company.

The authors thank Kern McNeill International, New Jersey, for contract research services.

Address for reprints: A.M. Storniolo, Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN 46285-2225.

Received July 9, 1998; revision received October 19, 1998; accepted October 19, 1998.

BACKGROUND. An Investigational New Drug (IND) treatment program allows patients access to a drug that has shown activity against a serious or life-threatening disease prior to full Food and Drug Administration (FDA) review and approval. This treatment IND program, in which patients with locally advanced or metastatic pancreatic carcinoma were treated with gemcitabine, began in 1995.

METHODS. Eligibility criteria were ≤1 prior chemotherapy regimen; a Karnofsky performance status (KPS) of ≥50; and adequate bone marrow, liver, and renal function. Gemcitabine was given at a dose of 1000 mg/m^2 weekly × 7 followed by a week of rest, then weekly × 3 every 4 weeks thereafter. In this program, disease-related symptom improvement (DRSI) was defined retrospectively as 1) improvement in pain (on a 7-point scale) and/or analgesic class (e.g., morphine improving to codeine) and/or KPS (≥20 points), or 2) stability of these three parameters with a 7% increase in weight from baseline.

RESULTS. A total of 3023 patients enrolled. At baseline, 80% of them had Stage IV disease, and 84% had a baseline KPS ≥ 70. The median age was 65 years, and 56% of the patients were male. The cumulative DRSI response rate after the fourth cycle was 18.4%. Of 982 patients with tumor response data, there were 14 with complete response and 104 with partial response, for an overall response rate of 12.0% (95% confidence interval [CI], 10.0–14.0%). For 2380 patients with survival data, the median survival was 4.8 months (95% CI, 4.5–5.1 months) and the 12-month survival was 15%. Gemcitabine was well tolerated; only 4.6% of discontinuations were due to adverse events.

CONCLUSIONS. Notable disease-related symptom improvement and survival were seen with gemcitabine in this large, compassionate-use setting, and these findings were in agreement with those of earlier registration trials. ***Cancer* 1999;85:1261–8.**
© 1999 American Cancer Society.

KEYWORDS: gemcitabine, pancreatic carcinoma, pain, performance status, disease-related symptom improvement, clinical benefit, survival, quality of life.

Patients with locally advanced and metastatic pancreatic carcinoma have a poor prognosis and suffer debilitating disease-related symptoms. Historically, single-agent 5-fluorouracil (5-FU) has been a frequently used treatment that has produced tumor response rates in the range of 0–19% (since 1985 when computed tomography [CT] assessment of tumor response became standard) and a median survival of 4.2–5.5 months.[1] A review of the literature on investigational new drugs (28 Phase II trials involving 25 agents) showed that, to date, there has been no improvement in patient outcome, with a median objective response rate of 0% (range, 0–14%) and a median survival of 3 months (range, 2–8.3 months).[2]

Gemcitabine (GEMZAR; Eli Lilly and Company, Indianapolis, IN) is a novel nucleoside analog with activity across a broad range of solid tumors.[3] The activity of gemcitabine in pancreatic carcinoma was assessed in early Phase II trials. In a United States study of 44 patients, Casper and colleagues reported an objective response rate of 11% and a median survival of 5.6 months.[4] In a European study of 34 patients, Carmichael and colleagues reported a tumor response rate of 6.3% and a median survival of 6.3 months.[5] Both study groups reported symptomatic improvements in their patients that were greater than suggested by the objective tumor response rates. These improvements were seen in pain (reductions in both pain severity and analgesic requirement) and in performance status. Two controlled registration studies were designed specifically to evaluate the effect of gemcitabine on disease-related symptoms. Both of these trials showed that about one-fourth of patients experienced improvement in disease-related symptoms.[6,1] This paper reports the results of a compassionate-use Investigational New Drug (IND) treatment protocol with the primary objective of providing treatment for pancreatic carcinoma patients and a secondary objective of collecting data from a large patient cohort representative of patients with pancreatic carcinoma in a typical clinical setting.

METHODS

The purpose of an IND treatment program, which is permitted by the Food and Drug Administration (FDA), is to facilitate the availability of promising new drugs to desperately ill patients as early in the drug development process as possible, before general marketing begins, and to obtain additional data on the drug's safety and effectiveness. There are four criteria for an IND treatment program: 1) The drug is intended to treat a serious or immediately life-threatening disease; 2) there is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population; 3) the drug is under investigation in a controlled clinical trial under an IND, or all clinical trials have been completed; and (4) the sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug with due diligence.

This IND treatment program involved 3023 patients and investigators at 882 study centers in the United States. Patients were treated between March 1995 and June 1996, at a time when the new drug application for gemcitabine (GEMZAR) was being reviewed by the FDA. Informed consent was obtained from all patients.

In this open-label, single-arm program, patients had to have histologic or cytologic diagnosis of locally advanced (Stage II or III) or metastatic (Stage IV) pancreatic carcinoma that was not amenable to surgery. Patients had to have received at most one prior chemotherapy regimen and no other form of cancer therapy in the 4 weeks preceding entry. Patients with radiosensitizing 5-FU were allowed into the program, because it was determined not to be chemotherapy in the true sense. Other inclusion criteria were adequate bone marrow reserve (leukocytes $\geq 3500 \times 10^6$/liter, thrombocytes $\geq 100{,}000 \times 10^6$/liter, hemoglobin $\geq$ 9g/dL, hematocrit $\geq$ 27%); adequate liver function (patients were excluded if they had bilirubin elevation $>$ 2.0 mg/dL or alanine transaminase/aspartate transaminase elevations $\geq$ 5 times the upper limit of normal) and renal function (patients were excluded if creatinine $>$ 1.5 mg/dL); calcium within 10% of normal; baseline Karnofsky performance status (KPS) $\geq$50; age $\geq$ 18 years; and life expectancy $\geq$ 12 weeks.

Gemcitabine (1000 mg/m^2) was administered intravenously over 30 minutes. During cycle 1, gemcitabine was given once weekly for up to 7 weeks, before a mandatory rest period of 1 week. In subsequent cycles, gemcitabine was given once weekly for 3 weeks, followed by a rest period of 1 week. Patients were allowed to remain on the study until disease progression or unacceptable drug toxicity was noted or until the patient or physician requested withdrawal. When gemcitabine was approved for marketing by the FDA (May, 1996), enrollment was closed, and all remaining patients were discontinued from the IND treatment program within 1 month, transferring their treatment to a nonexperimental setting.

Standard World Health Organization (WHO) criteria were used to assess tumor response in patients with measurable disease. Response assessments were made by individual investigators and were not subject to independent review. The patient's perception of average pain was scored monthly by the patient using a 7-point scale: 1 = none, 2 = slight, 3 = mild, 4 = moderate, 5 = moderately severe, 6 = severe, and 7 = unbearable. Analgesic requirement was scored by using a 6-point scale: 0 = no analgesics; 1 = aspirin, acetaminophen; 2 = codeine, propoxyphene, pentazocine/naloxone; 3 = oral hydromorphone, methadone, oxycodone/aspirin, morphine; 4 = parenteral opiates; and 5 = neurosurgical procedures.

Only one category was entered. In cases in which a patient took a combination of analgesics, the score corresponding to the drug(s) with the highest potency was generally entered.

After each cycle, the following assessments were made: KPS, analgesic requirement, average pain intensity, and occurrence and nature of any serious

TABLE 1
Patient Characteristics

Characteristic	No. of patients	Patients (%)
Gender		
Male	1401	56
Female	1098	44
Median age (yrs)	2501	65
Karnofsky performance status		
50	140	6
60	227	9
70	521	21
80	643	26
90	682	28
100	185	8
Disease stage		
II	177	7
III	316	13
IV	1989	80
Ethnic group		
Caucasian	2182	87
African American	199	8
Hispanic	84	3
Prior chemotherapy[a]		
None	1588	63
≥1	937	37

[a] Approximately 1% of patients in the program received more than one prior chemotherapy regimen for pancreatic carcinoma.

adverse events. When patients were discontinued from the study, the following assessments were made: best tumor response, time to death or progressive disease, and overall change in KPS and pain. If patients discontinued therapy for any reason other than death, then investigators were requested to provide 3 months' follow-up data.

To assess the composite treatment effect on symptoms, disease-related symptom improvement (DRSI) was assessed at the beginning of each cycle. DRSI was similar in intent to the clinical benefit response (CBR) measured in the registration trials of gemcitabine[7] but was determined retrospectively by using data points that would be collected routinely by physicians in the treatment of patients with pancreatic carcinoma. Patients were classified as DRSI responders if, compared with baseline, they had 1) an improvement in one or more of the following parameters (without any worsening in any other): pain and/or analgesic class (e.g., morphine improving to codeine), and/or KPS (≥20 points); or 2) stability compared with baseline in all three parameters described above plus an increase in weight of ≥7%. The following statistical methods were used: median Kaplan–Meier estimates and confidence intervals (CI)[8] for time-to-event variables and CIs[9] for tumor response rates.

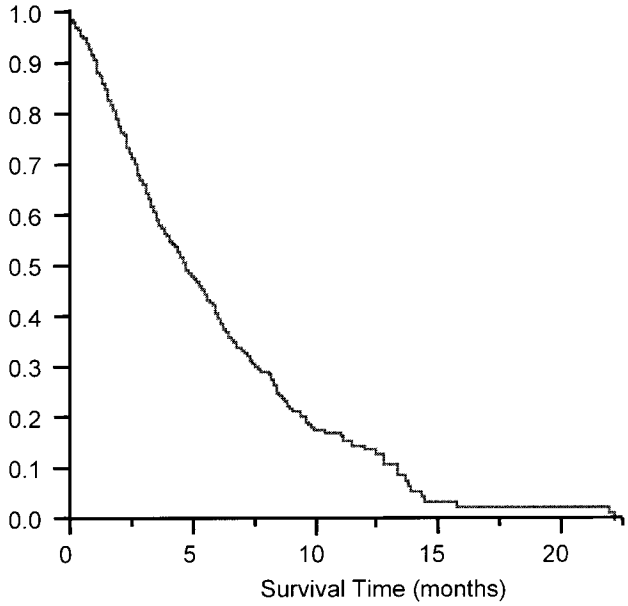

FIGURE 1. Kaplan–Meier survival curve (all patients, n = 2380).

RESULTS

Collection of Data

The IND treatment program involved 882 study centers and a total of 3023 patients. The program ran from March 1995 to June 1996. Given the nature of this program, the number of observations made for any given end point varied based on the number of completed records returned by the investigators. In the results reported below, patient numbers vary according to the specific data point in question.

Patient Population

Table 1 shows that the patients represented a standard sampling of patients with advanced pancreatic carcinoma: Eighty percent of patients entered with Stage IV disease, and 84% had a baseline KPS ≥ 70.

Gemcitabine Administration

For all patients in whom dosing data were recorded (n = 2015), the median dose of gemcitabine actually administered per visit was 1000 mg/m^2. The 10th and 90th percentiles were 905 and 1014 mg/m^2, respectively.

Survival

At the time of data cut off, survival data were available for 2380 patients; however, the survival times for 57% of these 2380 patients were censored (e.g., patients were lost to follow-up). Figure 1 shows the Kaplan–Meier survival curve for all patients. Median survival was 4.8 months (95% CI, 4.5–5.1 months). Probability

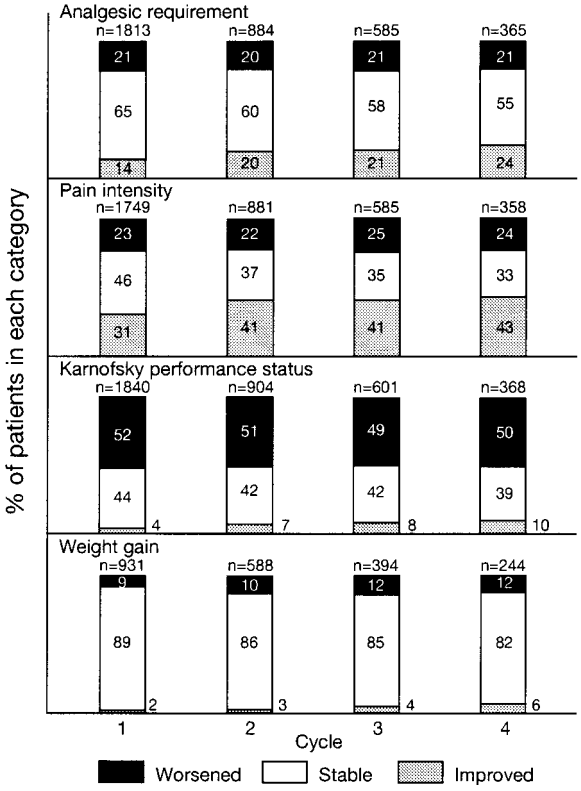

FIGURE 2. Change in disease-related symptoms with treatment.

of survival was 41% at 6 months, 22% at 9 months, and 15% at 12 months.

Disease Progression

At the time of data cut off, disease progression data were available for 2012 patients; however, the time to disease progression for 31% of these 2012 patients was censored. Median time to disease progression was 2.7 months (95% CI, 2.6–2.7 months).

Tumor Responses

At the time of data cut off, tumor response data were available for 982 patients. Response assessments were made by individual investigators and were not subject to independent review. There were 14 patients (1.4%) with complete responses and 104 patients (10.6%) with partial responses, for an overall response rate of 12.0% (95% CI, 10.0–14.2%).

Symptom Benefit

Figure 2 shows the changes in analgesic requirement, pain intensity, KPS, and weight. By the end of each of cycles 1–4, improvement in pain intensity of any amount was reported by 31%, 41%, 41%, and 43% of patients, respectively. These improvements in pain intensity were accompanied by changes in the class of analgesic required by patients, which improved in 14% of patients by the end of cycle 1 and in 20%, 21%, and 24% of patients by the end of cycles 2–4, respectively. Similarly, there were improvements in KPS in 4%, 7%, 8%, and 10% of patients by the end of cycles 1–4, respectively.

TABLE 2
Disease-Related Symptom Improvement[a]

Cycle completed	No. responders (%)
1	334 (13.5)
2	411 (16.6)
3	444 (18.0)
4	455 (18.4)

[a] Patients evaluated after four cycles.

The cumulative proportions of patients experiencing DRSI in the first four cycles are provided in Table 2. Patients who experienced DRSI at any given cycle were considered DRSI responders at all subsequent cycles. However, patients missing DRSI components for any reason (e.g., study discontinuation) were considered nonresponders. Hence, a total of 18.4% of patients had experienced DRSI by cycle 4.

Correlation of Efficacy Parameters to Baseline Factors

Efficacy parameters were analyzed by various patient factors measured at baseline, including prior chemotherapy status (none vs. one or more), disease stage (Stage II/III vs. Stage IV), age (age $\leq$ 65 vs. age $>$ 65), gender, and ethnic origin. Table 3 provides the results of this analysis, and Figures 3–5 show Kaplan–Meier survival curves by KPS, disease stage, and prior therapy, respectively.

The median survival was markedly longer in patients with KPS $\geq$ 70 than in patients with KPS $<$ 70 (5.5 vs. 2.4 months). Similarly, the median time to progression was longer in patients with KPS $\geq$ 70 than in patients with KPS $<$ 70 (2.9 vs. 1.7 months). Disease stage also was a prognostic factor for the time-to-event data. The median survival was longer in patients with Stage II/III disease than in those with Stage IV disease (6.6 vs. 4.4 months). Similarly, the median time to progression was longer in patients with Stage II/III disease than in patients with Stage IV disease (4.1 vs. 2.5 months). The median survival was higher in chemonaive patients (5.1 months) than in patients who had received prior therapy (4.4 months). Only disease stage had a prognostic correlation to DRSI response, and clinically significant symptom improvements were observed in all types of patient. Age, gen-

TABLE 3
Corelation of Efficacy to Baseline Factors[a]

Factor	Median survival time (mos)	Median time to disease progression (mos)	DRSI response after four cycles (%)	Best tumor response (CR+PR%)
Prior chemotherapy[b]				
None	5.1 (1489)[c]	2.8 (1268)	20 (1513)	13 (594)
≥1	4.4 (874)[c]	2.6 (744)	17 (882)	10 (388)
KPS				
≥70	5.5 (1963)[c]	2.9 (1649)[c]	19 (1983)	12 (854)
<70	2.4 (338)[c]	1.7 (291)[c]	18 (344)	10 (90)
Stage				
II/III	6.6 (472)[c]	4.1 (402)[c]	24 (477)[d]	12 (204)
IV	4.4 (1863)[c]	2.5 (1585)[c]	18 (1882)[d]	12 (764)
Age (yrs)				
≤65	4.8 (1169)	2.7 (987)	20 (1169)	10 (511)
>65	4.8 (1181)	2.8 (1012)	19 (1195)	14 (463)
Gender				
Female	4.9 (1035)	2.8 (885)	19 (1044)	13 (419)
Male	4.8 (1314)	2.6 (1113)	19 (1329)	11 (555)
Ethnic origin				
African American	4.9 (183)	2.5 (157)	19 (188)	11 (71)
Caucasian	4.8 (2060)	2.7 (1755)	19 (2078)	13 (856)
Hispanic	5.6 (77)	3.3 (61)	23 (78)	3 (31)

DRSI: disease-related symptom improvement; CR: complete response; PR: partial response; KPS: Karnofsky performance status.

[a] Sample size available for analysis is in parentheses.

[b] Approximately 1% of patients in the program received more than one prior chemotherapy regimen for pancreatic carcinoma.

[c] $P < 0.05$, log-rank test between prognostic factor strata.

[d] $P < 0.05$, chi-square test between prognostic factor strata.

der, and ethnic origin had no clinically significant effect on any of the patient outcomes.

Adverse Events

Discontinuation data were available for 2140 patients. Only 4.6% of these discontinuations were due to adverse events. Table 4 shows the most frequent events recorded in the serious adverse event database as of October, 1997. Apart from deaths and hospitalizations expected in patients due to progressive pancreatic carcinoma, the most serious adverse events were fever, pain, and asthenia. Vomiting, nausea, and nausea/vomiting each were reported in less than 4% of patients.

DISCUSSION

Patients with locally advanced or metastatic pancreatic carcinoma have a poor prognosis. Burris and colleagues[1] report that single-agent 5-FU produces tumor response rates ranging from 0% to 19% and a median survival of 4.2–5.5 months. Thus, the search goes on for new agents with improved activity in this disease.

Pancreatic carcinoma also is a particularly debilitating disease, producing pain in greater than 75% of patients, weight loss in 95%, anorexia in 64%, and nausea in 50% as well as depression, weakness, and impaired performance status in a significant number of patients.[10,11] Because most patients present with incurable disease, treatment is palliative, and symptom improvement assumes greater importance. The National Cancer Institute (NCI) and the FDA have accepted that the relief of tumor-related symptoms itself is a noteworthy goal of carcinoma treatment.[12] Pancreatic carcinoma provides an appropriate clinical setting in which to examine these alternative end points.

In an early trial of gemcitabine in pancreatic carcinoma, Casper et al. recognized the potential impact of treatment on tumor-related symptoms.[4] Those investigators found that a number of patients had a reduction in pain, were able to reduce their analgesic requirement, experienced an improvement in performance status, and were able to resume normal daily activities. Consequently, Eli Lilly and Company established two registration trials with the stated primary objective of assessing clinical benefit, a measure of disease-related symptoms, based on pain, KPS, and

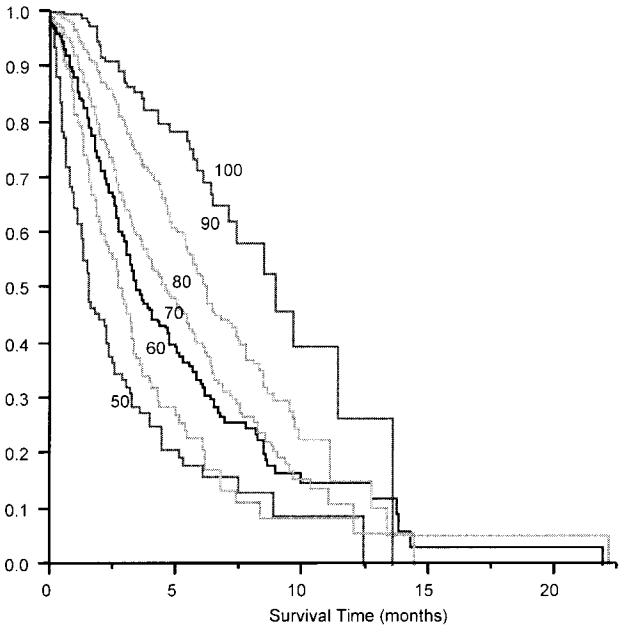

FIGURE 3. Kaplan–Meier curve survival by baseline Karnofsky performance status.

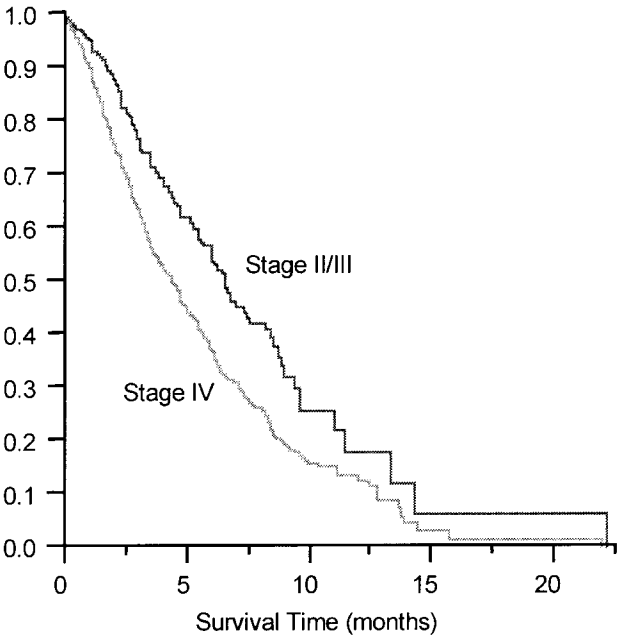

FIGURE 4. Kaplan–Meier curve survival by disease stage.

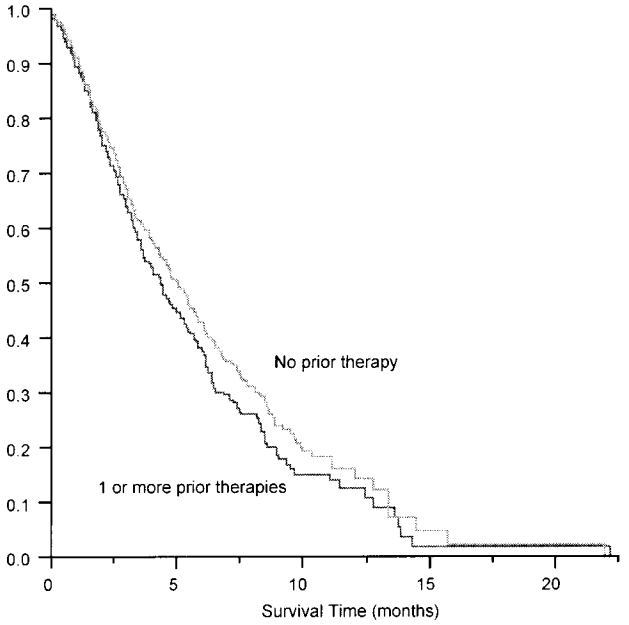

FIGURE 5. Kaplan–Meier curve survival by prior therapy.

TABLE 4
Toxicity Reported—Most Frequent Events Recorded in the Serious Adverse Event Database (3023 patients)[a]

Event term	No. of reports	Incidence (%)
Pancreatic carcinoma deaths and hospitalizations	1000	33.1
Fever	221	7.3
Pain	206	6.8
Asthenia	181	6.0
Abdominal pain	165	5.5
Dyspnea	151	5.0
Dehydration	137	4.5
Vomiting	119	3.9
Nausea and vomiting	119	3.9
Nausea	116	3.8
Anorexia	110	3.6
Surgical procedure[b]	106	3.5
Deep thrombophlebitis	98	3.2
Jaundice	96	3.2
Ascites	89	2.9
Edema	87	2.9
Anemia	84	2.8
Sepsis	73	2.4
Gastrointestinal hemorrhage	72	2.4

[a] Events reported irrespective of causality.

[b] Mostly surgery required for palliation of progressive pancreatic carcinoma, e.g., stent replacements for bile duct drainage or cholangitis, thoracentesis, pleural parencentesis.

dry weight gain. These trials showed that about one-quarter of patients were clinical benefit responders.[6,1] It was against this background that the IND treatment program was established to provide access to gemcitabine pending full FDA approval. This experience provided important information on the efficacy, toxicity, and tolerability of gemcitabine in a large number of patients treated in a community setting. Limited data collection requirements enabled 882 physicians to treat more than 3000 patients in a period of 16 months, an experience far more extensive than would

TABLE 5
Comparison of Gemcitabine Data in the Two Registration Trials and the Investigational New Drug Treatment Program

Factor	Single-arm study[6]	Randomized study[1]	Treatment IND
Patient population	5-FU refractory	Chemonaive	Up to 1 prior chemotherapy
No. patients	63	63 randomized to gemcitabine	3023 enrolled
Males/females (%)	51/49	54/46	56/44
KPS ≥ 70 (%)	79.3	82	84
Stage (%)			
II	2	14	7
III	11	14	13
IV	87	72	80
Median survival in mos (all patients)	3.9	5.7	4.8
Symptom improvement (%)			
CBR	27.0	23.8	—
DRSI	—	—	18.4

IND: investigational new drug; 5-FU: 5-fluorouracil; KPS: Karnofsky performance status; DRSI: disease-related symptom improvement; CBR: clinical benefit response.

have been possible through the conduct of a formal clinical trial.

The data collected were used in a composite measure of symptom palliation, which was termed DRSI. This measure is similar in intent to the CBR measured in the registration trials, but it has fewer specific requirements and, thus, was more feasible in such a broadly implemented program.

The baseline characteristics of patients in the two registration trials and the IND treatment program are similar (Table 5): About 80% of patients had Stage IV disease, and 84% had a KPS ≥ 70. This allows noteworthy comparisons to be made.

In the IND treatment program, 18.0% of 2471 patients were classified as DRSI responders after 4 months. In the two registration trials, CBR was seen in 23.8% and 27.0% of patients (Table 5). Although CBR and DRSI should not be compared directly, and although the two registration trials are not comparable with this IND treatment study, both CBR and DRSI suggest that gemcitabine does improve disease-related symptoms in a subset of patients under investigation. This is unlikely to be a placebo effect, because, in the randomized study, CBR was significantly greater ($P = 0.0022$) with gemcitabine (23.8%) than with 5-FU (4.8%).[1]

It is noteworthy that the improvement in pain intensity (Fig. 2) was seen in conjunction with a reduction in overall analgesic requirement, as suggested by a shift in the class of analgesics required to control pain (e.g., morphine to codeine). Both of these improvements are of real value to patients.

The median survival in chemonaive patients who were treated on this trial was 5.1 months, which is consistent with the survivals reported in gemcitabine-treated patients by Burris et al.[1] (5.7 months), Casper et al.[4] (5.6 months), and Carmichael et al.[5] (6.3 months). The median survival with gemcitabine in previously treated patients has been reported as 3.9 months, which is consistent with the finding of a 4.4-month median survival in this trial.[6]

In the IND treatment program, gemcitabine was well tolerated, with only 4.6% of discontinuations being due to toxicity. Only serious adverse advents were collected in the IND treatment program. WHO-graded toxicity profiles have been reported for the two pancreatic carcinoma registration trials[1,6]: manageable neutropenia (no neutropenic fever); thrombocytopenia (no Grade 4); nonspecific, flu-like symptoms (transient and treatable with acetaminophen); transient nausea and vomiting; and very little hair loss. An extensive safety overview for gemcitabine in 790 patients has been reported previously.[13] In addition to promising survival results and symptom improvement as measured by DRSI, objective responses also were observed by individual investigators in this IND treatment program.

Gemcitabine is the first new therapy for patients with advanced pancreatic carcinoma in more than 30 years. The results of this extensive IND treatment program support the positive survival and symptom improvement findings of the two registration trials. Studies to evaluate gemcitabine in patients with earlier stages of pancreatic carcinoma and to evaluate gemcitabine in combination with surgery, radiation, and other cytotoxic drugs have been initiated. These trials will help to further define, and possibly extend, the utility of this new antineoplastic drug against this devastating disease.

REFERENCES

1. Burris HA, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997;15:2403–13.
2. Rothenberg ML, Abbruzzese JL, Moore M, Portenoy RK, Robertson JM, Wanebo HJ. A rationale for expanding the endpoints for clinical trials in advanced pancreatic carcinoma. *Cancer* 1996a;78:627–32.
3. Von Hoff DD, Green MR, editors. Gemcitabine HCl: combined efficacy and tolerability in managing the solid tumor patient. *Semin Oncol* 1996;23(Suppl 10):1–100.

4. Casper ES, Green MR, Kelsen DP, Heelan RT, Brown TD, Flombaum CD, et al. Phase II trial of gemcitabine (2′2′-difluorodeoxycytidine) in patients with adenocarcinoma of the pancreas. *Invest New Drugs* 1994;12:1229–34.
5. Carmichael J, Fink U, Russell RCG, Spittle MF, Harris AL, Spiessi G, et al. Phase II study of gemcitabine in patients with advanced pancreas cancer. *Br J Cancer* 1996;73:101–5.
6. Rothenberg ML, Moore MJ, Cripps MC, Andersen JS, Portenoy RK, Burris HA, et al. A phase II trial of gemcitabine in patients with 5-FU-refractory pancreas cancer. *Ann Oncol* 1996b;7:347–53.
7. Andersen JS, Burris HA, Casper E, Clayman M, Green M, Nelson RL, et al. Development of a new system for assessing clinical benefit for patients with advanced pancreatic cancer [abstract 1600]. *Proc Am Soc Clin Oncol* 1994;13:461.
8. Efron, B. Censored data and the bootstrap. *J Am Stat Assoc* 1981;76:312–19.
9. Leemis LM, Trivedi KS. A comparison of approximate interval estimators for the Bernoulli parameter. *Am Stat* 1996; 50(1):63–8.
10. Alter CL. Palliative and supportive care of patients with pancreatic cancer. *Semin Oncol* 1996;23:229–40.
11. Howard JM, Jordan GL Jr. Cancer of the pancreas. *Curr Prob Cancer* 1977;2(3):1–52.
12. O'Shaughnessy JA, Wittes RE, Burke G, Friedman MA, Johnson JR, Neiderhuber JE, et al. Commentary concerning demonstration of safety and efficacy of investigational anticancer agents in clinical trials. *J Clin Oncol* 1991;9:2225–32.
13. Green MR. Gemcitabine safety overview. *Semin Oncol* 1996; 23(5-Suppl 10):32–5.