Activity of Gemcitabine in Patients with Advanced Pancreatic Carcinoma

A Review

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BACKGROUND. In early phase II trials in advanced pancreatic cancer, gemcitabine demonstrated modest antitumor activity. The investigators in these studies reported that gemcitabine should be studied further in view of the degree and frequency of symptomatic improvement observed, the durability of some of the remissions, and the favorable toxicity profile.

METHODS. In order to quantify such symptomatic improvement, a rigorous endpoint of Clinical Benefit was developed that incorporated measures including pain intensity, analgesic consumption and performance status, which have been shown to be reliable and valid endpoints in other studies.

RESULTS. Two trials have been conducted using this methodology in patients with advanced pancreatic carcinoma.

CONCLUSIONS. The results of these studies suggest that gemcitabine is the first cytotoxic agent with any meaningful impact on survival and disease-related symptoms in advanced pancreatic adenocarcinoma. The degree of improvement seen is one which patients with cancer often consider to be most important. Further studies will be required to define more fully the role of gemcitabine in the treatment of pancreatic cancer. ***Cancer* 1996; 78:633–8.** © *1996 American Cancer Society.*

KEYWORDS: advanced pancreatic carcinoma, gemcitabine, clinical benefit, disease-related symptoms, pain, performance status, quality of life.

Pancreatic adenocarcinoma is the fifth most common cause of cancer death in North America. The initial symptoms are usually nonspecific abdominal complaints that can be observed with a variety of benign conditions. Eventually the patient develops more severe pain, weight loss, or jaundice and it is at this time that the diagnosis is usually made. A cure is only possible by surgical removal of the primary tumor, but this is rarely achieved in practice. However, by the time a diagnosis is made only a small fraction of patients are resectable. Few etiologic factors have been identified and there is no defined high risk group in whom increased surveillance might detect lesions at an earlier stage. At present, pancreatic cancer has the worst 5-year survival rate of any form of cancer.

Meaningful improvements in the treatment of adenocarcinoma of the pancreas will only come from better systemic therapies. The results obtained to date with cytotoxic chemotherapy have been very disappointing. Recent editorials and review articles about chemotherapy have even questioned whether further studies should be carried out.[1–3] A significant effort in testing new drugs for activity against pancreatic cancer has occurred over the past 10 years. A review of

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the published literature over the past 3 years reveals that over 40 Phase II studies of new agents and new combinations have been reported.[4] None have demonstrated a response rate > 20%, which is the usual standard that must be met for further testing to be done. A review of such studies demonstrates both the difficulties that pancreatic cancer presents and the lack of substantive improvements that have been observed to date. It gives support to the general pessimism that exists about the treatment of pancreatic cancer at the present time.

It is generally accepted that there is no particularly effective chemotherapy for patients with pancreatic cancer. Whether a standard chemotherapy currently exists is an area of debate. Opinions range from palliative treatment with no chemotherapy, to single agent 5-fluorouracil (5-FU), to a 5-FU based combination regimen. Phase II studies of 5-FU and 5-FU-based combinations have reported response rates in the range of 0 to 43%. However, no agents have been shown to have reproducible response rates > 15%. The differences in response rates are most likely due to a combination of patient selection and differing response criteria. A single Phase II study is not adequate to allow conclusions to be drawn about the activity of a drug against pancreatic cancer, and in general, a positive result in one study has not been reproduced in subsequent studies. Modulation of 5-FU with leucovorin, which has been useful in colorectal cancer, has not been shown to be of any value.

Whether 5-FU-based combination chemotherapy is any better than 5-FU alone is doubtful. Certainly no randomized trial has demonstrated that combination therapy is superior. While the addition of other agents like mitomycin C, doxorubicin, or cisplatin to 5-FU may not improve response rate or survival they will certainly increase the severity and extent of the toxicity. This is a very relevant concern with a disease that makes patients quite ill and the benefits of therapy are modest.

A more realistic estimate of the value of 5-FU and 5-FU-based combinations can be obtained from larger multi-institutional Phase III studies where these therapies were used (Table 1).[15–21] These trials confirm the poor outlook for patients with pancreatic cancer and the minimal impact of treatment on survival. None showed any statistically significant improvements in survival. In only 1 arm of 1 trial was a response rate of > 20% observed.[5] This was to streptozotocin, mitomycin C, and 5-FU (SMF). However, 3 other trials that used SMF as a treatment arm reported response rates of 4, 10, and 14%. Therefore, while on occasion a patient may be helped by chemotherapy, no treatment has had any consistent or meaningful effects on the burden of disease that these patients are enduring.

TABLE 1
Randomized Trials in Advanced Pancreatic Carcinoma (Only Studies with More than 50 Patients Are Included)

	Responses (%)	Median survival (mos)	Reference
5-FU + CCNU	N/S	3	15
Best supportive care		3.9	
Melphalan	1/43 (2)	1.8	16
5-FU, methyl CCNU	4/41 (10)	3.3	
5-FU, methyl CCNU, streptozotocin	3/43 (7)	2.9	
Mi-C, 5-FU	5/60 (8)	4.1	5
SMF	19/56 (34)	4.2	
5-FU	[a]	5.1	17
5-FU, doxorubicin		4.7	
FAM		4.7	
SMF	3/66 (4)	4.2	18
FAM	9/63 (14)	6.1	
FAM	4/29 (14)	2.7	19
SMF	4/28 (14)	4	
SMF (modified)	4/27 (15)	3.1	
5-FU	(7)[a]	4.5	20
5-FU, doxorubicin, cisplatin	(15)	3.5	
5-FU, Mi-C, methotrexate, cyclophosphamide, vincristine	(21)	4.5	
SMF	4/49 (10)	10	21
Cisplatin, Ara-C, caffeine	2/38 (5)	5	

[a] The majority of patients in these studies did not have measurable disease.
5-FU: 5-fluorouracil; CCNU: lomustine; Mi-C: mitomycin C; FAM: 5-FU, doxorubicin, mitomycin C; SMF: streptozotocin, mitomycin C, 5-FU; N/S: not significant.

Patients with advanced pancreatic cancer are often quite ill at the time a decision about treatment is being made. Many are malnourished with weight loss that can be due to gastric outlet obstruction, pancreatic insufficiency, and cancer-related cachexia. Concurrent medical problems due to pain and a hypercoaguable state are also common. If a decision is made to treat such a patient, then the primary purpose is palliation of symptoms. If treatment is associated with significant toxicity, then any beneficial effects on the disease may be lost due to the side effects of treatment. While a temporary palliation of symptoms may seem a rather modest goal in a patient dying of malignant disease, it is one that patients consider important.[6] If a cytotoxic drug has limited effect on the visible size of the cancer but does lead to some improvements in quality of life, performance status, or disease-related

symptoms, then it would be valuable. None of the chemotherapy regimens tested in the past has been reproducibly shown to improve the quality of life for patients with advanced pancreatic cancer. Palliative endpoints such as quality of life scales, or measurement of symptoms and performance status have rarely been used in pancreatic cancer trials. In a recent article, Van Cutsem and Fevery[7] argue that the evaluation of symptomatology and quality of life should be a priority and, in future pancreatic cancer trials, these should be used to accompany classical efficacy measures like tumor response and survival.

STUDIES WITH GEMCITABINE IN PATIENTS WITH PANCREATIC CANCER

Gemcitabine (2',2'-difluorodeoxycytidine; dFdC) is a novel nucleoside analog with structural similarities to cytosine arabinoside (ara-C). However, unlike ara-C, gemcitabine has significant antitumor activity against a variety of solid tumor cell lines in vitro, including pancreatic and other gastrointestinal tumors. Like ara-C, gemcitabine requires intracellular activation to its triphosphate derivative which is incorporated into DNA and then inhibits DNA synthesis via a process of masked DNA chain termination. Gemcitabine has other intracellular effects which may contribute to its cytotoxic activity; these include inhibition of ribonucleotide reductase, stimulation of deoxycytidine kinase (the enzyme responsible for gemcitabine activation), and inhibition of deoxycytidine monophosphate (dCMP) deaminase (the primary enzyme responsible for gemcitabine degradation).[8,9]

Preclinical studies established that a schedule of gemcitabine given once a week for 3 weeks followed by a week of rest provided a combination of activity and acceptable tolerability. Therefore a dosage and schedule of 800–1000 mg/m^2 given weekly $\times$ 3 every 4 weeks was chosen for most Phase II studies. Phase I studies of the weekly schedule did include patients with pancreatic cancer who had failed other chemotherapy. In one trial a patient with pancreatic cancer had a partial response of several months with an associated improvement in disease-related symptoms and performance status.

A large number of Phase II studies of weekly gemcitabine has now been performed. Evidence of activity has been observed in nonsmall cell lung cancer, breast cancer, bladder cancer, and ovarian cancer. Separate Phase II studies of weekly gemcitabine on patients with pancreatic cancer were carried out in the U.S. and Europe.[10,11] In both studies the primary objective was to measure the objective response rate to gemcitabine in patients with measurable disease.

The American study was conducted at 3 centers, the Memorial Sloan-Kettering Cancer Center, the University of California, San Diego, and the University of Texas, San Antonio. Patients were required to have pathologic confirmation of advanced pancreatic adenocarcinoma, no prior chemotherapy, an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1, and normal hematologic parameters.[10] Patients were also required to have a serum creatinine ≤ 1.5 mg/dl (< 133 μM), a serum bilirubin ≤ 1.5 mg/dl (< 26 μM), and a prothrombin time < 12 seconds. The treatment plan was for a dosage of 800 mg/m^2 to be given once weekly for 3 of 4 weeks (one treatment cycle). Dose escalation by 25% in subsequent cycles was prescribed in the absence of dose-limiting toxicity, to a maximum dosage of 1500 mg/m^2. Information about the effects of gemcitabine on disease symptoms or performance status was collected by individual investigators but formal symptom scale or quality of life measures were not used. Forty-four patients entered into the study and 35 of these received at least 2 cycles of gemcitabine. The median age was 63 years, 35 of 44 were performance status 1 (ECOG) and the majority were treated at Memorial Sloan-Kettering Cancer Center. All had measurable disease with 12 having Stage II or III disease and the remaining 32, visceral spread, which in all but 1 case included metastases in the liver. Partial responses were observed for 5 of 44 patients (11%). In addition, 14 patients (32%) had stable disease for > 4 months. The duration of response in the 5 patients who had a partial response was 4+, 8, 13, 17, and 20+ months. Some degree of symptomatic improvement was observed in all 5 responding patients and in 9 of those with stable disease. The median survival was 5.6 months with 23% of the patients alive at 1 year. The drug was well tolerated. Most patients continuing in the study were escalated to 1000 mg/m^2, and 10 were escalated to 1250 mg/m^2. In the 2 patients escalated to 1500 mg/m^2, severe flu-like symptoms were observed which necessitated subsequent dosage reduction. These symptoms were observed at the lower dosages, but were mild and well controlled with acetaminophen. The authors concluded that while there was marginal activity as expressed by the partial response rate, further study of this drug in patients with pancreatic cancer was definitely warranted. This conclusion was based on observations on the degree and frequency of symptomatic improvement, the durability of some of the remissions, and the favorable toxicity profile. They also noted that most patients could tolerate a dosage of 1000 mg/m^2 or possibly greater in this weekly schedule.

The European study had entry criteria that were somewhat less restrictive.[11] Patients were required to have pathologic confirmation of advanced pancreatic adenocarcinoma, no prior chemotherapy, an ECOG performance status of ≤ 2, and normal hematologic parameters. A minor degree of renal impairment was allowed (creatinine < 150 μm or 1.7 mg/dl), as was some degree of hepatic impairment (bilirubin $<$ twice normal, AST $< 3 \times$ normal). The initial plan was for a dosage of 800 mg/m^2 to be given once weekly for 3 of 4 weeks. There was minimal toxicity with this schedule and after 6 patients, the starting dose was increased to 1000 mg/m^2. As well as assessing the effects of gemcitabine on tumor size, some preliminary information was collected on performance status, analgesic consumption, and pain intensity. In about half of the patients the serum markers CA19-9, carcinoembryonic antigen (CEA), and CA19-5 were also serially measured. Thirty-four patients entered on study, with the majority (61%) having metastatic disease, primarily in the liver. A partial response was observed in 2 of 32 evaluable patients (6.3%) and 6 (18.8%) had stable disease for > 4 weeks. All responses determined by investigators were validated by an external oncology review board. An improvement in performance status for $\geq$ 4 weeks was observed in 17.2% of the patients, 7.4% had improvement in analgesic consumption, 28% had an improvement in pain intensity and 27% had an improvement in their nausea. Patients were only evaluable in each of these categories if they had some degree of impairment at the start of the study. Symptomatic improvement in these categories lasted for approximately 8 to 12 weeks. Gemcitabine was well tolerated with $< 10\%$ experiencing Grade 4 neutropenia or thrombocytopenia, no episodes of febrile neutropenia, and no patient having Grade 4 nonhematologic toxicity. The only Grade 3 nonhematological toxicity observed with any frequency was nausea and vomiting (26.7%), which in some cases was probably disease related. The median survival was 6.3 months. While there was only quite modest evidence of activity observed in this trial, the observations of symptomatic improvement in a larger group of patients was consistent with that observed in the U.S. study.

The Phase II studies of gemcitabine in patients with pancreatic cancer demonstrated that this drug was well-tolerated but had a tumor response rate similar to that observed in other Phase II trials. However, several investigators noted that a proportion of patients felt better on treatment, despite not meeting the criteria for a partial response. As gemcitabine did seem to provide useful palliation for some patients, and the goal of any treatment of metastatic pancreatic cancer is palliative, 2 further studies were planned. The first was a Phase III study comparing weekly gemcitabine to weekly 5-FU in patients with locally advanced or metastatic pancreatic adenocarcinoma who had never received chemotherapy. The second was a Phase II study in patients who had progressed while receiving 5-FU. In these studies a measure of disease palliation (the "clinical benefit") was the primary endpoint. The rigorous measurement of clinical benefit[12] incorporates pain intensity, analgesic consumption, performance status, and weight. To be considered a responder a patient must have ≥ 1 of the following: a 50% decrease in pain intensity, a 50% decrease in analgesic consumption, or a $\geq$ 20-point increase in performance status that is sustained for ≥ 4 weeks without deterioration in any of the other parameters. For patients who are stable in pain intensity, analgesic consumption, and performance status, a 7% increase in dry body weight is required for the patient to be classified a responder. During the study, pain intensity is measured daily by the patient using a 10 cm linear analog scale; analgesic consumption is based on a daily diary kept by patients; performance status is measured weekly by 2 independent individuals with the lower of the 2 scores counted, and weight is measured weekly by the study nurse. While clinical benefit was a novel endpoint, it was rigorous, and incorporated measures that have been shown to be reliable and valid in other studies. The development of this clinical benefit endpoint also reflected a growing emphasis on the use of assessments such as quality of life instruments, and disease related symptom scores as measures of palliation in the therapy of patients with advanced cancer.

In the study in 5-FU-refractory patients gemcitabine was given at a dosage of 1000 mg/m^2 weekly for up to 7 weeks followed by a week of rest and then once weekly for 3 of 4 weeks.[13] Sixty-three patients entered the study. All patients had progressive disease on 5-FU, and had some degree of symptoms related to their disease. The median Karnofsky performance status was 70, the median analgesic consumption was 60 mg morphine per day, and the median baseline pain intensity score was 29 (range: 3–68), 0 being no pain and 100, the worst possible pain. The incidence of serious toxicity was low with only 1 patient experiencing Grade 4 toxicity. Clinical benefit was experienced in 17 of 63 patients (27%).

In the Phase III study, 126 patients with histologically confirmed advanced or metastatic adenocarcinoma of the pancreas were randomized to gemcitabine 1000 mg/m^2 weekly for up to 7 weeks followed by a week of rest, and then weekly $\times$ 3 every 4 weeks

thereafter, or to 5-FU 600 mg/m^2 over 30 minutes once weekly.[14] Patients had not received any prior chemotherapy and had to have measurable or evaluable disease. Patients on both treatment arms were balanced in terms of gender, age, and disease stage, with approximately 75% having Stage IV or metastatic disease. Clinical benefit was the primary endpoint: 23.8% of the gemcitabine patients experienced clinical benefit versus only 4.8% of the 5-FU patients ($P = 0.0022$). The median survival for gemcitabine patients was 5.65 months and for 5-FU was 4.41 months ($P = 0.0025$). Twenty-four percent of gemcitabine patients and 6% of the 5-FU patients were alive at 9 months; and 18% of gemcitabine patients and 2% of the 5-FU patients were alive at 12 months. Toxicity was graded according to the World Health Organization (WHO) criteria. Neutropenia $\geq$ Grade 3 was observed in 23% of gemcitabine patients and 5% of 5-FU patients. However, there were no episodes of febrile neutropenia requiring hospitalization. WHO $\geq$ Grade 3 nonhematological toxicity (nausea and vomiting or diarrhea) was observed in 15% of the gemcitabine patients and 10% of the 5-FU patients.

These two new studies confirm the observations of symptomatic improvement in a reasonable proportion of patients that was observed in the earlier Phase II studies. Clinical benefit, defined as a major improvement in pain intensity, analgesic consumption, or performance status, was observed in 27% of the 5-FU-refractory patients and in 24% of the chemotherapy naive patients. In addition there was a highly statistically significant survival advantage associated with the use of gemcitabine in comparison with patients treated with 5-FU.

SUMMARY

Gemcitabine is the first cytotoxic agent that has been demonstrated to have any meaningful impact on either survival or disease related symptoms in pancreatic adenocarcinoma. The benefits observed with the use of gemcitabine in pancreatic cancer are admittedly modest, however, the degree of improvement observed is one which patients with cancer consider to be important. Further studies will be required to more fully define the role of gemcitabine in the treatment of pancreatic cancer. These will include the use of gemcitabine as an adjuvant to surgical resection. Also, gemcitabine is a potent radiosensitizer in preclinical models and clinical studies are ongoing to explore its effectiveness and tolerability in combination with external beam radiation therapy in patients with locally advanced disease. Progress in the fight against pancreatic cancer is likely to be slow. However, gemcitabine has shown value in providing palliation against many of the important symptoms of disease. The experience gained in doing the gemcitabine studies will also be of assistance as we look at other approaches to cancer treatment in the future.

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