Tumori, 90: 192-195, 2004

TREATMENT OF METASTATIC PANCREATIC CANCER WITH A COMBINATION OF GEMCITABINE AND 5-FLUOROURACIL: A SINGLE CENTER PHASE II STUDY

Ozkan Kanat, Turkkan Evrensel, Ender Kurt, Mutlu Demiray, Guzin Gonullu, Murat Arslan, and Osman Manavoglu

Department of Medical Oncology, Faculty of Medicine, Uludag University, Bursa, Turkey

***Aim*: To determine the activity and toxicity of a combination of weekly gemcitabine and 5-fluorouracil bolus intravenously in patients with metastatic pancreatic cancer.**
***Patients and methods*: Twenty-one patients with previously untreated metastatic pancreatic cancer were included in this phase II study. The schedule was gemcitabine (1000 mg/m^2 iv) and 5-fluorouracil (500 mg/m^2 bolus iv) weekly for 3 weeks every month.**
***Results*: Four patients (19%) achieved a partial response and three stable disease. A clinical benefit was obtained in 7 patients (33%). Median survival for all the patients was 6 months. The treatment was well tolerated and toxicity was mild. WHO grade 3 leukopenia occurred in 2 (9.5%) patients, grade 3 anemia in 4 (19%) patients, grade 3-4 thrombocytopenia in 4 (19%) patients, grade 1 diarrhea in 1 (4.7%) patient and grade 1 mucositis in 3 (14.2%) patients.**
***Conclusion*: The weekly administration of gemcitabine combined with 5-fluorouracil bolus iv is an active and well-tolerated regimen in metastatic pancreatic cancer. However, its efficacy is relatively limited.**

Key words: chemotherapy, gemcitabine, 5-fluorouracil, pancreatic cancer.

Introduction

Metastatic pancreatic cancer (MPC) is a very aggressive and highly lethal disease. The median survival of patients with MPC is approximately 3 to 6 months. It is one of the neoplasm most resistant to chemotherapy. For this reason, the medical management of the disease presents a considerable therapeutic challenge to the oncologist. Many chemotherapy drugs have been tested in the treatment of MPC, and the results have been disappointing. However, clinical trials have demonstrated that chemotherapy may alleviate some disease-related debilitating symptoms, such as pain, weight loss and fatigue, and may improve the patient's quality of life.

5-Fluorouracil (5-FU) is the most extensively studied and most widely used agent in the treatment of MPC. It is the standard care for patients with MPC. However, the results obtained with this agent remain dismal, with reported response rate ranging up to 20%[1]. Gemcitabine (GEM), a novel nucleoside analog, is one of the most promising drugs in the treatment of this patient population. In a phase II study conducted in the United States, GEM was administered at doses of 800 to 1250 mg/m^2 per week to 44 patients with advanced pancreatic cancer. GEM not only achieved an objective response rate of 11%, but also a median survival of 5.6 months and a remarkably high 1-year survival rate (23%)[2]. In a European study of 34 patients, Carmichael *et al.*[3] achieved a response rate of 6.3% and a median survival of 6.2 months. Furthermore, both study groups reported symptomatic improvements (pain and performance status) in their patients.

Rothenberg *et al.*[4], in a phase II study, examined the role of GEM treatment in 63 patients with 5-FU-refractory pancreatic cancer. Seventeen patients (27%) experienced a clinical benefit response (CBR) to GEM. The median survival was 3.85 months, with an objective response rate of 10.5%. Such data suggested that there was a lack of clinical cross-resistance between 5-FU and GEM.

The novel mechanism of action and therapeutic efficacy, combined with a lack of clinical cross-resistance to 5-FU, make GEM an obvious candidate for combination therapy with 5-FU in the treatment of MPC. Therefore, we decided to combine weekly bolus GEM and 5-FU to treat patients with MPC in a phase II trial.

Patients and methods

Patient selection

Patients with histologically or cytologically confirmed, bidimensionally measurable metastatic adenocarcinoma of the pancreas were eligible for the study. Other eligibility criteria included the following: age 18 years or older; Karnofsky performance status (KPS) 60-100; no prior chemotherapy or hormone therapy; adequate bone marrow (leukocyte count >4000/mm^3, absolute neutrophil count 1500/mm^3, and platelet count >100,000/mm^3), kidney (creatinine 1.5 mg/dL), liver (bilirubin 1.5 mg/dL and transaminase levels 3 times the upper normal limit 5 times for patients with liver metastasis), and cardiac functions. Patients were to have a life

Correspondence to: Ozkan Kanat, MD, Uludag University Faculty of Medicine Department of Medical Oncology, Gorukle 16059, Bursa, Turkey. Tel +90-224-4428400; fax +90-224-4428049; e-mail ozkanat@uludag.edu.tr

Received July 7, 2003; accepted September 8, 2003.

expectancy of at least 2 months. Patients could have received prior radiation therapy for symptom palliation, providing it was completed at least 4 weeks before enrollment.

The following patients were excluded: pregnant or lactating patients and patients with brain metastasis or uncontrolled concurrent medical disease. Written informed consent was obtained from all patients.

Pretreatment evaluation included a complete medical history, clinical examination, ECG, complete blood count, complete biochemistry survey, serum CEA and CA-19-9 determinations, chest X-ray, computed tomographic scan of the chest, abdomen and pelvis, and other imaging studies if necessary.

Chemotherapy

Antiemetics, including 5-HT_3 antagonists, were administered before chemotherapy according to institutional policy. GEM was diluted in normal saline and administered intravenously (iv) over 30 mins at the dose of 1000 mg/m^2 once weekly for 3 consecutive weeks. 5-FU was given as an iv bolus at the dose of 500 mg/m^2 once weekly for 3 consecutive weeks immediately after GEM. A new cycle started on day 28 if the absolute neutrophil and platelet counts were at least 1500/mm^3 and 100000/mm^3, respectively. If these values were not reached at the scheduled retreatment, therapy was delayed by weekly intervals. If after a delay of 2 weeks these hematological criteria were still not met, the patient was removed from the study. The weekly doses of GEM were reduced by 25% within the cycle if absolute neutrophil count was less than 500/mm^3 or if the platelet count was less than 50000/mm^3. If the patient developed mucositis, diarrhea, or hand-foot syndrome of grade 1 or 2 severity, the dose of 5-FU was reduced by 20%.

Tumor response was assessed every two cycles. Chemotherapy continued until there was evidence of disease progression, or until there was significant clinical deterioration because of tumor-related symptoms.

Analgesic consumption, weight changes and KPS were recorded at initial consultation, at each clinical visit and weekly during chemotherapy. Complete blood count and serum biochemistry were measured weekly.

Toxicity was evaluated and graded according to WHO criteria[5]. Tumor response was also classified according to WHO criteria. CBR was evaluated using the criteria previously defined in the evaluation of GEM in pancreatic cancer[4,6,7]. A patient was defined as a clinical benefit responder or nonresponder on the basis of the analgesic consumption, KPS, and weight change (Table 1). A patient was considered a clinical benefit responder if there was sustained improvement (>4 weeks) in any of the above parameters without deterioration in the others.

Time to progression and overall survival were calculated from the date of entry into study until disease progression or death or last observation using the Kaplan-Meier method[8].

Table 1 - Clinical benefit scale*

Parameter
Analgesic consumption
Positive (reduced): a decrease of 50% in analgesic consumption from baseline for patients with baseline analgesic consumption = 10 mg morphine-equivalent per day
Negative (increased): any increase in the use of analgesics
Stable: any other result Karnofsky performance status:
Positive (improved): = 20 point increase over baseline for patients with A baseline score of 70 or less
Negative (worsening): A decrease of at least 20 points from baseline
Stable: any other resultWeight:
Positive: an increase in weight of 7% over baseline, excluding third space fluid
Negative: any other result
Clinical benefit response: sustained (= 4 weeks) improvement in at least one parameter without worsening in any other

*Adapted from Burris *et al.*[7]

Results

A total of 21 patients (15 males and 6 females) with a median age of 60 years (range, 40-72) entered the study. The median KPS was 70 (range, 60-100). Patient characteristics are listed in Table 2. Eight patients underwent palliative bypass procedures. At presentation, all patients had experienced weight loss and 16 complained of pain (14 of them were taking analgesics). A total of 85 cycles of chemotherapy were administered (median, 4 cycles per patient). All patients were assessable for response and toxicity. There was no complete response. A partial response was obtained in 4 patients (19%). Three patients (14%) achieved stable disease. In total, 7 patients improved in at least one parameter of analgesic consumption, weight or KPS without simultaneous deterioration in any of the other parameters. Therefore, the clinical benefit ratio was 33%.

Increased pretreatment serum CEA and CA-19-9 levels were present in 15 (71.4%) and 20 (95.2%) patients, respectively. Levels of CEA and CA-19-9 were decreased or remained within pretreatment levels in 1 (4.7%) and 3 (14.2%) patients, respectively.

The median time to progression was 3 months, median survival was 6 months (95% CI, 2.6-9.3; range, 3-

Table 2 - Patient characteristics

No. of patients	21
Age (yr)	
Median	60
Range	40-72
Sex	
M/F	15/6
Karnofsky performance status	
60-80	18
80-100	3
Sites of metastatic disease	
Liver	17
Lung	1
Peritoneum	6
Bone	1

12), and the 1-year survival rate was 4.7%. The regimen was well tolerated. Treatment-related toxicity is summarized in Table 3. We observed grade 3 leukopenia in 2 (9.5%) patients, grade 3 anemia in 4 (19%) patients, grade 3-4 thrombocytopenia in 4 (19%) patients, grade 1 mucositis in 3 (14%) patients and grade 1 diarrhea in 1 (4.75%) patient.

Discussion

Chemotherapy for MPC has only limited value in clinical practice. This disease is less chemo-sensitive than other commonly occurring solid malignancies. Several chemotherapeutic drugs have been tested in the treatment of MPC. 5-FU is the most extensively studied and most widely used drug for the disease, using a variety of doses and schedules of administration. Response rates with the drug have ranged from 0% to 20%[1]. Biochemical modulation of 5-FU with leucovorin or interferon and various combinations of 5-FU, doxorubucin, and mitomycin-C have also failed to yield better results[9]. These disappointing results obtained with single agent 5-FU or combination regimens emphasize the need for new, more effective agents for the treatment of pancreatic cancer.

GEM is currently one of the most promising new agents in the treatment of MPC. In a phase II study conducted by Burris *et al.*[6], 126 previously untreated patients were randomized to GEM or bolus 5-FU. A CBR was reported in 23.8% of patients treated with GEM and 4.8% of those treated with 5-FU ($P = 0.0022$). The median survival was 5.65 months for patients treated with GEM and 4.61 months for those treated with 5-FU ($P = 0.0025$), with objective response rates of 5.4% and 0% respectively. The survival rate at 1 year was 18% for GEM-treated patients and 2% for 5-FU-treated patients. The study demonstrated that GEM was more effective than 5-FU in alleviation of disease-related symptoms in patients with advanced pancreatic cancer. GEM also conferred a modest survival advantage over treatment with 5-FU. However, despite its superior activity, the results achieved with single-agent GEM in pancreatic cancer are relatively poor[2,4].

We evaluated the feasibility and efficacy of GEM administered for 3 weeks every 4 weeks in combination with bolus 5-FU in patients with MPC. To date, there is a wealth of published reports of phase I-II studies of GEM in combination with 5-FU alone or with 5-FU modulated with leucovorin for the treatment of pancreatic cancer. Although the dose and schedule of administration of GEM have been similar in nearly all the studies, the administration of 5-FU varies from protracted continuous infusion to 24-hr continuous infusion or weekly bolus infusion at differing dose levels. The efficacy of fluoropyrimidines is highly schedule dependent in gastrointestinal cancer, and weekly bolus administration as in our treatment might not be the optimal schedule. However, continuous 5-FU infusion treatment is not convenient, since it necessitates the use of a permanent central venous access and a portable pump system. In contrast to findings in patients with colorectal cancer, the addition of leucovorin does not appear to provide any therapeutic advantage over single-agent 5-FU in patients with pancreatic cancer. Recent phase II trials have evaluated high-dose leucovorin (500 mg/m^2) administered daily or as a continuous infusion for six days in combination with 5-FU[10,11]. The daily dose of 5-FU ranged from 375 mg/m^2 to 600 mg/m^2. The results were disappointing: objective response rates averaged less than 10%, and toxicity was often significant. Therefore we did not modulate the 5-FU administration with leucovorin in the present study.

The response rate was relatively lower (19%) in our trial than that obtained with the regimen in other trials. In spite of the low objective response rate, 33% of patients treated in our trial achieved sustained improvement in pain, KPS or weight loss. Therapy was well tolerated. We observed WHO grade 4 hematological toxicity in one (4.7%) patient and WHO grade 3 in 9 (42.8%) patients. No grade 3 or 4 non-hematological toxicity was observed.

Using the same doses and schedule for GEM/5-FU, De Gusmao *et al.*[12] reported a partial response in 6 of 14 patients (42.9%), and 7 patients (50%) achieved a CBR. In this small series, no WHO grade 3 or 4 toxicity was observed.

In another phase II study, Murad *et al.*[13] treated 17 patients with advanced pancreatic cancer and 5 patients with biliary tract cancer using the same doses and schedule for GEM/5-FU. They achieved a 30.8% overall response rate. The median survival for all patients was 9 months. A CBR was recorded in 42.8% of patients. The regimen was very well tolerated. They observed grade 3 neutropenia in 11% of cycles, grade 3 mucositis in 7% of cycles, and grade 3 diarrhea in 10% of cycles. One patient developed reversible WHO grade 4 febrile neutropenia. The authors concluded that the regimen has encouraging activity and mild toxicity profile in these chemo-resistant tumors.

In a phase II trial of 54 patients with advanced pancreatic cancer, Cascinu *et al.*[14] administered GEM at a dose of 1000 mg/m^2 for 3 consecutive weeks and 5-FU as an iv bolus at a dose of 600 mg/m^2 on the same days as GEM. A partial response was obtained in 2 patients, and 34 patients achieved stable disease. In spite of the low response rate (3.7%), a CBR was recorded in 28 patients (51%). The median survival was 7 months. No grade 3-4 toxicity was observed.

Table 3 - Maximum toxicity observed for each patients (n = 21)

Side effect	Grade 1	Grade 2	Grade 3	Grade 4
Leukopenia	2	3	2	-
Anemia	1	4	4	-
Thrombocytopenia	3	3	3	1
Mucositis	3	-	-	-
Diarrhea	1	-	-	-

In conclusion, the favorable toxicity profile and the convenience of administration are the major advantages of the combination of GEM and 5-FU given by this schedule. Its efficacy is limited but compares well with other chemotherapy treatment options in MPC. Current attempts to combine GEM with newer agents such as capecitabine, UFT, taxanes and irinotecan in the treatment of the MPC might improve the results of chemotherapy.

References

1. Schnall SF, Macdonald JS: Chemotherapy of adenocarcinoma of the pancreas. Semin Oncol, 23: 220-228, 1996.
2. Casper ES, Green MR, Kelsen DP, Heelan RT, Brown TD, Flombaum CD, Trochanowski B, Tarassoff PG: Phase II trial of gemcitabine (2,2'-difluorodeoxycytidine) in patients with adenocarcinoma of the pancreas. Invest New Drugs, 12: 29-34, 1994.
3. Carmichael J, Fink U, Russell RC, Spittle MF, Harris AL, Spiessi G, Blatter J: A phase II trial of gemcitabine in patients with advanced pancreatic cancer. Br J Cancer, 73: 103-105, 1996.
4. Rothenberg ML, Moore MJ, Cripps MC, Andersen JS, Portenoy RK, Burris HA 3rd, Green MR, Tarassoff PG, Brown TD, Casper ES, Storniolo AM, Von Hoff DD: A phase II trial of gemcitabine in patients with 5-FU-refractory pancreas cancer. Ann Oncol, 7: 347-353, 1996.
5. World Heath Organization: Handbook for reporting results of cancer treatment. WHO offset publication number 48. World Health Organization, Geneva, 1979.
6. Burris HA 3rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD, Von Hoff DD: Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreatic cancer: a randomized trial. J Clin Oncol, 15: 2403-2413, 1997.
7. Burris H, Storniolo AM: Assessing clinical benefit in the treatment of pancreas cancer: gemcitabine compared to 5-fluorouracil. Eur J Cancer, 33 (Suppl 1): 18-22, 1997.
8. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc, 53: 457-481, 1958.
9. Arbuck SG: Overview of chemotherapy for pancreatic cancer. Int J Pancreatol, 7: 209-222, 1990.
10. Crown J, Casper ES, Botet J, Murray P, Kelsen DP: Lack of efficacy of high-dose leucovorin and fluorouracil in patients with advanced pancreatic adenocarcinoma. J Clin Oncol, 9: 1682-1686, 1991.
11. DeCaprio JA, Mayer RJ, Gonin R, Arbuck SG: Fluorouracil and high-dose leucovorin in previously untreated patients with advanced adenocarcinoma of the pancreas: results of a phase II trial. J Clin Oncol, 9: 2128-2133, 1991.
12. de Gusmao CBRA, Murad AM, Scalabrini-Neto AO: Phase II trial of the use of gemcitabine (G) and 5-fluorouracil (5-FU) in the treatment of advanced pancreatic (APC) and biliary tract (ABTC) adenocarcinoma. Proc ASCO, 17: A1116, 1998.
13. Murad AM, Guimaraes RC, Aragao BC, Rodrigues VH, Scalabrini-Neto AO, Padua CA, Moore FC: Phase II trial of the use of gemcitabine and 5-fluorouracil in the treatment of advanced pancreatic and biliary tract cancer. Am J Clin Oncol (CCT), 26: 151-154, 2003.
14. Cascinu S, Silva RR, Barni S, Labianca R, Frontini L, Piazza E, Pancera G, Giordani P, Giuliodori L, Pessi MA, Fusco V, Luporini G, Cellerino R, Catalano G: A combination of gemcitabine and 5-fluorouracil in advanced pancreatic cancer, a report from the Italian Group for the Study of Digestive Tract Cancer (GISCAD). Br J Cancer, 80: 1595-1598, 1999.