

Gemcitabine Combined With Uracil-Tegafur in Patients With Advanced Pancreatic Cancer

Ugur Coskun, MD; Necati Alkis, MD; Gokhan Celenkoclu, MD; Süleyman Buyukberber, MD; Metin Ozkan, MD; Celalettin Camci, MD; Aytug Uner, MD; Ozlem Er, MD; Ulkü Yalcintas Aslan, MD; Alper Sevinc, MD; Saadet Tokluoglu, MD; Banu Ozturk, MD; Ramazan Yildiz, MD; Mustafa Benekli, MD; for Anatolian Society of Medical Oncology

The aim of the study was to evaluate the efficacy and tolerability of gemcitabine and uracil-tegafur (UFT) combination in patients with advanced pancreatic carcinoma, retrospectively. Thirty-one patients, including 27 with metastatic disease, were treated with gemcitabine at a dose of 1000 mg/m² in 30 minutes on days 1 and 8, and oral UFT 300 mg/m² on days 1-14, as the first-line regimen in advanced stage. The cycle was repeated every 21 days. A total of 116 cycles of chemotherapy were administered, with a median of 3 cycles per patient (range 1-13). The objective response rate was observed in 6 (19.3%) patients with 1 (3.2%) complete response, and 5 (16.1%) partial responses. The median response duration was 4 (range, 3-14) months. Eight (25.8%) patients had a standard deviation of more than 3 months. Median overall survival was 8 months (95% CI, 6-10 months) and median time to progression was 4.2 months (95% CI, 1-6 months). This combination was generally well tolerated. There were no life-threatening side effects. Most common toxicities were of hematologic and gastrointestinal nature. In conclusion, this regimen was well tolerated and seemed to have a moderate activity in the palliative treatment of advanced pancreatic carcinoma.

Keywords: drugs ■ pancreas ■ cancer ■ metastasis

J Natl Med Assoc. 2009;101:761-764

Author Affiliations: Gazi University Medical School, Departments of Medical Oncology (Drs Coskun, Buyukberber, Uner, Ozturk, Yildiz, and Benekli), Ankara Oncology Hospital (Drs Alkis, Celenkoclu, Aslan, and Tokluoglu), Ankara, Turkey; Erciyes University Medical School, Departments of Medical Oncology (Drs Ozkan, Kayseri, and Er) Turkey; Gaziantep University Medical School, Departments of Medical Oncology (Drs Camci and Sevinc), Gaziantep, Turkey.

Corresponding Author: Ugur Coskun, MD, Department of Medical Oncology, Gazi University Medical School, Besevler, Ankara 06500, Turkey (ugurcos@hotmail.com).

INTRODUCTION

Pancreatic carcinoma has increased in incidence over the past several decades.¹ Despite recent progress in imaging modalities, approximately

80% of patients with pancreatic adenocarcinoma have nonresectable disease at the time of diagnosis due to either invasion in adjacent tissues or the presence of distant metastases.² Therefore, more than 90% of patients with cancer of the pancreas may be candidates for systemic chemotherapy either at diagnosis or after relapse.³ Most of the studies with 5-fluorouracil (5-FU), cisplatin, doxorubicin, mitomycin-C, and the nitrosoureas have yielded disappointing results with an objective response in about 10% to 20% of cases and a median survival of 6 to 7 months.^{4,5} However, 2 randomized trials showed that chemotherapy prolongs survival about 4 months, compared to supportive care alone.^{6,7}

Gemcitabine is a prodrug that requires intracellular phosphorylation by the enzyme deoxycytidine kinase and conversion to the active difluorodeoxycytidine diphosphate and triphosphate forms.^{8,9} Gemcitabine has demonstrated significant clinical activity in patients with pancreatic adenocarcinoma, but the results as a single agent yields only a 5.4% objective response rate with a median survival of 5.7 months.¹⁰ Single-agent gemcitabine became standard therapy for advanced pancreas cancer 10 years ago.¹¹ A phase I-II trial of gemcitabine combined with 5-FU in continuous infusion obtained better results, an overall response rate of 19% and a median survival of 10 months.¹²

Uracil-tegafur (UFT), an oral fluoropyrimidine, is a combination of tegafur (1-(tetrahydrofuryl)-5-fluorouracil) and uracil in a molar ratio of 1:4.³ UFT has been found to be as effective as continuous infusion of 5-FU with a better toxicity profile in various solid tumors.^{13,14}

In the present study we retrospectively evaluated the activity and toxicity profile of gemcitabine combined with oral UFT.

PATIENTS AND METHODS

We retrospectively evaluated the file records of 31 patients treated with gemcitabine and UFT combination in the first-line setting of advanced pancreatic cancer. During the treatment, 27 (87.1%) of patients had metastatic disease and 4 (12.9%) patients had inoperable

locally advanced disease. Two patients had a history of surgery and 3 had previous radiotherapy (one as adjuvant setting, 2 for locally advanced disease). Treatment consisted of intravenous infusion of gemcitabine 1000 mg/m² in 30 minutes on days 1 and 8, and oral UFT 300 mg/m² on days 1-14. The cycle was repeated every 21 days. Doses were reduced by 50% if patients experienced leucopenia (white blood cell count [WBC] <1500/ μ L) and thrombocytopenia (platelets <100 000/ μ L). Chemotherapy was omitted if the WBC count was less than 1000/ μ L and platelets less than 50 000/ μ L. Treatment was stopped if disease progression or major toxicities occurred or according to physician's decision.

The median age was 60 years (range, 34-70). Twenty-two (71%) patients were male and 9 (29%) patients were female.

The inclusion criteria were as follows: patients with histologically confirmed pancreatic adenocarcinoma; Eastern Cooperative Oncology Group (ECOG) performance status 0-2; clinically measurable disease defined as bidimensionally measurable lesions, adequate bone marrow (WBC >3 \times 10⁹/L, platelets >100 \times 10⁹/L, hemoglobin >10 g/dL), liver (total bilirubin <2 mg/dL, aspartate aminotransferase or alanine aminotransferase <3 times upper limit of normal), and renal (blood urea nitrogen <30 mg/dL, creatinine <1.5 times upper limit of normal); no history of other malignancies and age 20 to 70 years. Patients who had received radiotherapy were entered provided that measurable lesions were outside of radiotherapy fields. Patients with brain metastases were ineligible.

Responses to treatment were evaluated after every 2 cycles by computed tomography of the abdomen or the radiological examinations that detected the disease at other sites. Responders were defined as complete response (disappearance of assessable disease) or partial

response (reduction of >50% of the lesion of the 2 largest tumor diameters). Stable disease meant less than a 25% increase in tumor size. Progressive disease was defined by an increase of more than 25% in tumor size.

Statistical Analysis

The overall survival time was calculated as the period from the start of chemotherapy until death from any cause or until the date of the last follow-up. Overall survival times were estimated by the Kaplan-Meier method.

RESULTS

Characteristics of patients and responses to chemotherapy are shown in Table 1. Median overall survival was 8 months (95% CI, 6-10 months) (Figure). Median time to progression was 4.2 months. (95% CI, 1-6 months).

A total of 116 cycles of chemotherapy were administered, with a median of 3 cycles per patient (range, 1-13). The objective response rate was observed in 6 (19.3%) patients with 1 (3.2%) complete response and 5 (16.1%) partial responses. The median response duration was 4 (range, 3-14) months. Eight (25.8%) patients had stable disease more than 3 months.

Adverse events are shown in Table 2. Neutropenia (all grades) was reported by 13 (41.9%) patients, including 2 (6.5%) grade 3 neutropenia. Thrombocytopenia was reported by 8 (25.8%) patients, including 1 grade-3 toxicity. Grade 3 nausea and vomiting were reported by 2 (6.5%) patients. Grade 4 diarrhea was reported by 1 patient (3.2%). Febrile neutropenia were not observed.

DISCUSSION

Although 2 studies reported that chemotherapy improves survival of patients with pancreatic cancer compared to best supportive care, the results are very disappointing.^{6,7} The development of more effective che-

Table 1. Characteristics of Patients and Response Rates

Characteristics	n (%)	Responses (%)			
		Complete Response	Partial Response	Stable Disease	Progressive Disease
Total	31	1 (3.2)	5 (16.1)	8 (25.8)	17 (54.8)
Gender					
Male	22 (71)	1 (4.5)	2 (9)	7 (31.8)	12 (54.5)
Female	9 (29)	0 (0)	3 (33.3)	1 (11.1)	5 (55.6)
Performance status					
0-1	27 (87.1)	1 (3.7)	5 (18.5)	6 (22.2)	15 (55.6)
2	4 (12.9)	0 (0)	0 (0)	2 (50)	2 (50)
Stage					
Locally advanced	4 (12.9)	0 (0)	1 (25)	1 (25)	2 (50)
Metastatic	27 (87.1)	1 (3.7)	4 (14.8)	7 (25.9)	15 (55.5)
Sites of distant metastasis					
None	4 (12.9)	0 (0)	1 (25)	1 (25)	2 (50)
Liver only	16 (51.6)	0 (0)	3 (18.8)	4 (25)	9 (56.2)
Liver plus other	6 (19.4)	1 (16.7)	1 (16.7)	1 (16.7)	3 (49.9)
Other	5 (16.1)	0 (0)	0 (0)	2 (40)	3 (60)

motherapy drugs and regimens is required to improve the dismal prognosis of pancreatic cancer.

Gemcitabine is a widely used agent for the treatment of advanced pancreatic cancer and has served as the standard of chemotherapy for recent years,¹⁵ but the results obtained with single-agent gemcitabine are still poor, with a median survival of 5.6 months and a response rate of 5.4%.¹⁰ To increase its activity, recent studies have combined gemcitabine with either bolus or infusional 5-FU. A response rate of 19% and a median overall survival of 10 months were reported with the combination gemcitabine with infusional 5-FU and a response rate of 4%, and a median survival of 7 months was reported with the combination of gemcitabine with bolus 5-FU.^{12,16} However, a recent study did not show any improvement in prognosis of patients with the combination of gemcitabine and 5-FU compared to gemcitabine alone in advanced pancreatic cvarcinoma.¹⁷ It was also suggested that the continuous administration of oral fluoropyrimidines in combination with gemcitabine may improve the results of gemcitabine alone.^{3,18,19} Erlotinib is a small-molecule tyrosine kinase inhibitor (TKI) of the human epidermal growth factor receptor (EGFR). The survival advantage of erlotinib was demonstrated in a multicenter, randomized, phase III clinical study, in combination with gemcitabine, in patients with locally advanced or metastatic pancreatic adenocarcinoma.²⁰

The inconvenience of continuous 5-FU administration has recently forced some investigators to evaluate the role of oral fluoropyrimidines. In a study, UFT alone has been reported to have no activity in metastatic pancreatic cancer.²¹ In another study, an objective response of 9.5% has been reported with single-agent capecitabine in patients with advanced pancreatic cancer.²² In a study reported by Feliu et al,² in which gemcitabine 1200 mg/m² at a fixed-dose rate was combined with oral UFT 400 mg/m²/day (on days 1-21) with 28 days' interval, a 33% response rate and a median survival of 11 months were reported in 43 patients advanced pancreatic cancer, including 35 metastatic patients. In the present study, median overall survival was 8 months and the objective response rate was observed in 6 (19.3%) patients, including 1 (3.2%) complete response and 5 (16.1%) partial responses. Additional 8 (25.8%) patients had stable disease more than 3 months. Although the results were somewhat worse than that reported by Feliu et al,² they are comparable with those achieved in a study by Lee et al,⁸ combining gemcitabine 1000 mg/m² for 30 min once weekly for 3 consecutive weeks and oral UFT 390 mg/m²/day on days 1-14 with 28 days' interval, which reported an objective response rate of 22.7% and a median survival of 5.8 months in 22 patients with metastatic pancreatic adenocarcinoma (100%). In our study, the chemotherapy regimen (gemcitabine 1000 mg/m² in 30-min infusion; UFT,

Figure. Overall Survival of Patients

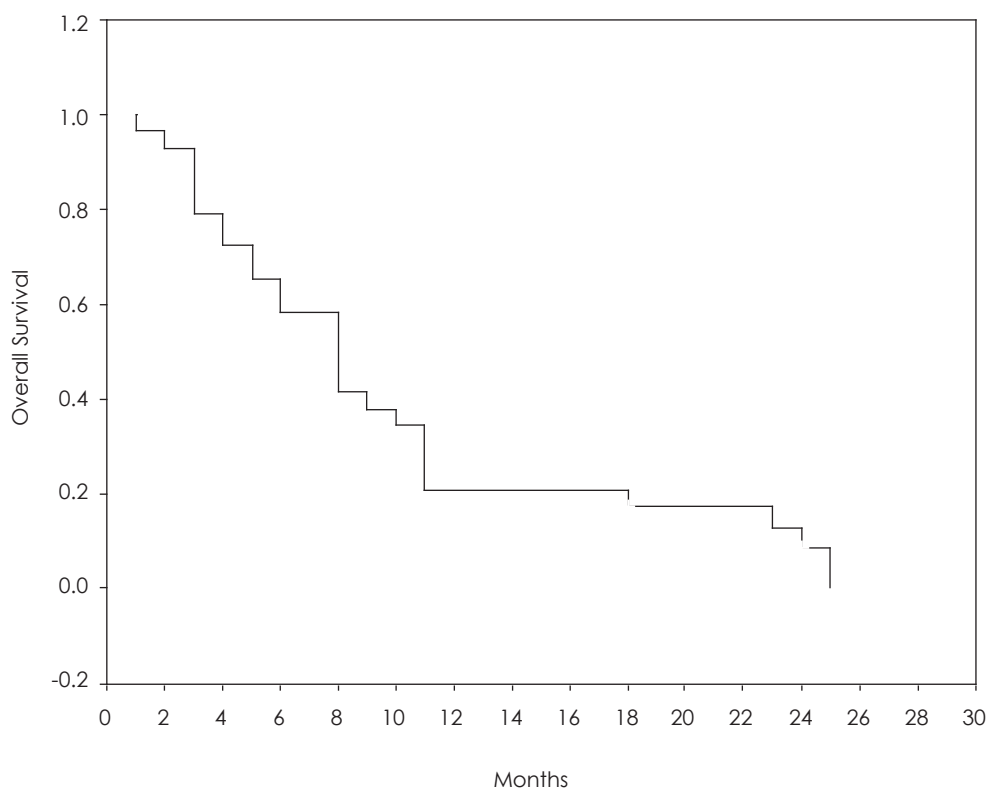


Table 2. Common Toxicities

Toxicity	No. of Patients (%)	
	All Grades	Grade 3/4
Neutropenia	13 (41.9)	2 (6.5)
Thrombocytopenia	8 (25.8)	1 (3.2)
Diarrhea	10 (32.3)	1 (3.2)
Nausea/vomiting	13 (41.9)	2 (6.4)
Stomatitis	2 (6.4)	0 (0)
Asthenia	5 (16.1)	0 (0)

1-14 days) and the patient population (90% metastatic disease) looked similar to Lee's study⁸ in contrast to Feliu's study,² in which a higher infusion dose for gemcitabine (1200 mg/m²) with fixed-dose rate infusion and longer duration of UFT therapy (on days 1-21) were used in patients with pancreatic cancer, including 35 (81%) metastatic patients. This can be a possible explanation for the different response rates and median survivals among these studies. The use of fixed-dose rate for gemcitabine would be more effective than its short time infusion, which was used in our and Lee's studies.⁸

This combination was generally well tolerated. There were no life-threatening side effects. Most common toxicities were hematologic, including neutropenia (41.9%) and thrombocytopenia (25.8%); and gastrointestinal, including nausea/vomiting (41.9%) and diarrhea (32.3%), which were mostly mild. A dose reduction was required only in 5 (16.1%) of patients, because of grade 3 and 4 toxicities. Although the number of patients with poor performance status is only 4 in this study, none of objective responses were seen in this group. In accordance with the literature, patients with good performance status had better results and better tolerability in the study.

In conclusion, this regimen was well tolerated and seemed to be convenient and moderately active in the palliative treatment of advanced pancreatic carcinoma. To increase the activity, different dose schedules or administration of the drugs such as a fixed-dose rate infusion of gemcitabine should be investigated in larger studies.

REFERENCES

- Silverman DT, Schiffman M, Everhart J, et al. Diabetes mellitus, other medical conditions and familial history of cancer as risk factors for pancreatic cancer. *Br J Cancer*. 1999;80:830-1837.
- Feliu J, Mel R, Borrega P, et al. Oncopaz cooperative group, Spain. Phase II study of a fixed dose-rate infusion of gemcitabine associated with uracil/tegafur in advanced carcinoma of the pancreas. *Ann Oncol*. 2002;13:1756-1762.
- Feliu J, Lopez Alvarez MP, Jaraiz MA, et al. Phase II trial of gemcitabine

- and UFT modulated by leucovorin in patients with advanced pancreatic carcinoma. The ONCOPAZ Cooperative Group. *Cancer*. 2000;89:1706-1713.
- Sporn JR. Practical recommendations for the management of adenocarcinoma of the pancreas. *Drugs*. 1999;57:69-79.
 - Schnall SF, Macdonald JS. Chemotherapy of adenocarcinoma of the pancreas. *Semin Oncol*. 1996;23:220-228.
 - Glimelius B, Hoffman K, Sjoden PO, et al. Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer. *Ann Oncol*. 1996;7:593-600.
 - Palmer KR, Kerr M, Knowles G, Cull A, Carter DC, Leonard RC. Chemotherapy prolongs survival in inoperable pancreatic carcinoma. *Br J Surg*. 1994;81:882-885.
 - Lee J, Park JO, Kim WS, et al. Phase II study of gemcitabine combined with uracil-tegafur in metastatic pancreatic cancer. *Oncology*. 2004;66:32-37.
 - Huang P, Chubb S, Hertel LW, Grindey GB, Plunkett W. Action of 2',2'-difluorodeoxycytidine on DNA synthesis. *Cancer Res*. 1991;51:6110-6117.
 - Burris HA 3rd, Moore MJ, Andersen J, 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;15:2403-2413.
 - Burris H 3rd, Rocha-Lima C. New therapeutic directions for advanced pancreatic cancer: targeting the epidermal growth factor and vascular endothelial growth factor pathways. *Oncologist*. 2008;13:289-298.
 - Hidalgo M, Castellano D, Paz-Ares L, et al. Phase III study of gemcitabine and fluorouracil as a continuous infusion in patients with pancreatic cancer. *J Clin Oncol*. 1999;17:585-592.
 - Van Cutsem E, Peeters M. Oral fluoropyrimidines in colorectal cancer. *Semin Oncol*. 2000;27:91-95.
 - Sulkes A, Benner SE, Canetta RM. Uracil-florafur: an oral fluoropyrimidine active in colorectal cancer. *J Clin Oncol*. 1998;16:3461-3475.
 - Takamori H, Kanemitsu K, Tsuji T, et al. 5-fluorouracil intra-arterial infusion combined with systemic gemcitabine for unresectable pancreatic cancer. *Pancreas*. 2005;30:223-226.
 - Cascinu S, Silva RR, Barni S, et al. 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*. 1999;80:1595-1598.
 - Berlin JD, Catalano P, Thomas JP, Kugler JW, Haller DG, Benson AB 3rd. Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern Cooperative Oncology Group Trial E2297. *J Clin Oncol*. 2002;20:3270-3275.
 - Oettle H, Riess H. Gemcitabine in combination with 5-fluorouracil with or without folinic acid in the treatment of pancreatic cancer. *Cancer*. 2002;95:912-922.
 - Cascinu S, Frontini L, Labianca R, et al. A combination of a fixed dose rate infusion of gemcitabine associated to a bolus 5-fluorouracil in advanced pancreatic cancer, a report from the Italian Group for the Study of Digestive Tract Cancer (GISCAD). *Ann Oncol*. 2000;11:1309-1311.
 - Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol*. 2007;25:1960-1966.
 - Ueno H, Okada S, Okusaka T, Ikeda M, Kuriyama H. Phase II study of uracil-tegafur in patients with metastatic pancreatic cancer. *Oncology*. 2002;62:223-227.
 - Cartwright TH, Cohn A, Varkey JA, et al. Phase II study of oral capecitabine in patients with advanced or metastatic pancreatic cancer. *J Clin Oncol*. 2002;20:160-164. ■