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ORIGINAL REPORT

Randomized Phase II Study of Gemcitabine Administered at a Fixed Dose Rate or in Combination With Cisplatin, Docetaxel, or Irinotecan in Patients With Metastatic Pancreatic Cancer: CALGB 89904

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See accompanying editorial on page 5487 and articles on pages 5499, 5513, and 5660

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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose
The relative value of gemcitabine-based combination chemotherapy therapy and prolonged infusions of gemcitabine in patients with advanced pancreatic cancer remains controversial. We explored the efficacy and toxicity of gemcitabine administered at a fixed dose rate or in combination with cisplatin, docetaxel, or irinotecan in a multi-institutional, randomized, phase II study.

Patients and Methods
Patients with metastatic pancreatic cancer were randomly assigned to one of the following four regimens: gemcitabine 1,000 mg/m^2 on days 1, 8, and 15 with cisplatin 50 mg/m^2 on days 1 and 15 (arm A); gemcitabine 1,500 mg/m^2 at a rate of 10 mg/m^2/min on days 1, 8, and 15 (arm B); gemcitabine 1,000 mg/m^2 with docetaxel 40 mg/m^2 on days 1 and 8 (arm C); or gemcitabine 1,000 mg/m^2 with irinotecan 100 mg/m^2 on days 1 and 8 (arm D). Patients were observed for response, toxicity, and survival.

Results
Two hundred fifty-nine patients were enrolled onto the study, of whom 245 were eligible and received treatment. Anticipated rates of myelosuppression, fatigue, and expected regimen-specific toxicities were observed. The overall tumor response rates were 12% to 14%, and the median overall survival times were 6.4 to 7.1 months among the four regimens.

Conclusion
Gemcitabine/cisplatin, fixed dose rate gemcitabine, gemcitabine/docetaxel, and gemcitabine/irinotecan have similar antitumor activity in metastatic pancreatic cancer. In light of recent negative randomized studies directly comparing several of these regimens with standard gemcitabine, none of these approaches can be recommended for routine use in patients with this disease.

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INTRODUCTION

Pancreatic adenocarcinoma is resistant to many systemic therapies and continues to be a leading cause of cancer-related death.[1] The administration of single-agent gemcitabine has been a mainstay of pancreatic cancer treatment based on evidence of clinical benefit and prolongation of survival when compared with fluorouracil in patients with advanced disease.[2] However, objective tumor responses after treatment with gemcitabine occur in less than 10% of patients, and median survival times are usually less than 6 months.

Combining gemcitabine with a second systemic agent has seemed to be a logical way to potentially enhance response rates and survival times for patients with advanced pancreatic cancer. This approach has unfortunately met with only limited success. A combination of gemcitabine and erlotinib was associated with a modest improvement in survival (hazard ratio for death = 0.82; $P = .038$) when compared with gemcitabine alone. However, the addition of the erlotinib was also associated with a higher incidence of rash, diarrhea, and hematologic toxicity.[3] In the preliminary report of a randomized study comparing gemcitabine and capecitabine with gemcitabine alone in 533 patients, the gemcitabine/capecitabine combination was associated with an enhanced overall response rate (14.2% *v* 7.1%, respectively) and a modest improvement in median survival time (7.4 *v* 6 months, respectively).[4] The

final report of a similar study, however, failed to demonstrate a significant survival advantage in the capecitabine-containing arm.[5]

Both irinotecan and docetaxel have been reported to have modest single-agent activity in pancreatic cancer.[6-8] Single-arm studies combining either of these agents with gemcitabine demonstrated their safety and showed preliminary evidence of promising activity.[9,10] Similarly, the combination of gemcitabine and cisplatin was associated with encouraging antitumor activity, with a reported overall response rate of 11% in a phase II study comprising 41 pancreatic cancer patients.[11] A fourth approach, modulating gemcitabine by administration at a fixed dose rate, was developed as an alternative technique to potentially increase the efficacy of gemcitabine.[12] After intravenous administration, gemcitabine undergoes intracellular phosphorylation to its active triphosphate metabolite, 2′,2′-difluoro 2′-deoxycytidine triphosphate.[13] The rate of formation of this metabolite is dose rate dependent and can be increased through the use of prolonged infusions, thereby enhancing its cytotoxic effect.

To further evaluate the efficacy and toxicity of gemcitabine-based chemotherapy regimens in pancreatic cancer, we performed a randomized phase II study of three different gemcitabine-based combinations or fixed dose rate infusion gemcitabine in patients with advanced pancreatic cancer, with the goal of identifying a promising regimen to take forward into a formal phase III study. Two hundred fifty-nine patients were randomly assigned to receive either gemcitabine/cisplatin, fixed dose rate gemcitabine, gemcitabine/docetaxel, or gemcitabine/irinotecan. Patients were observed for the primary end point of overall survival (OS) at 6 months. Secondary end points included toxicity, radiologic response, biochemical (CA 19-9) response, and time to tumor progression (TTP).

PATIENTS AND METHODS

Patient Characteristics

Eligible patients for this study were required to have biopsy-documented pancreatic adenocarcinoma, with evidence of distant metastatic disease. Patients with locally advanced disease without metastases were not eligible. Prior adjuvant therapy with fluorouracil and/or radiation therapy was allowed if such treatment had been completed at least 2 weeks before registration. All patients were age ≥ 18 years and had Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, adequate hematologic function, creatinine ≤ 1.5 mg/dL, total bilirubin ≤ 1.5 mg/dL, AST ≤ 2.5× upper limit of normal (ULN), and alkaline phosphatase ≤ 2.5× ULN if AST was more than 1.5× ULN (alkaline phosphatase of any value was accepted if AST ≤ 1.5× ULN). This protocol was reviewed by the institutional review board of each participating center, and all patients provided written informed consent before participation in the study.

Trial Structure and Organization

Patient registration and data collection were managed by the Cancer and Leukemia Group B (CALGB) Statistical Center. Data quality was ensured by careful review of data by CALGB Statistical Center staff and by the study chair. All analyses were performed by CALGB statisticians based on the study database frozen on March 11, 2008.

Treatment Plan

Patients were randomly assigned to receive one of the following four regimens: gemcitabine/cisplatin (arm A), fixed dose rate gemcitabine (arm B), gemcitabine/docetaxel (arm C), or gemcitabine/irinotecan (arm D). Initial dosing regimens were as follows. In arm A, gemcitabine was administered as a 30-minute infusion at a dose of 1,000 mg/m^2 on days, 1, 8, and 15, every 28 days. Cisplatin was administered over 30 minutes at a dose of 50 mg/m^2 on days 1 and 15, every 28 days. In arm B, gemcitabine was administered at a dose of 1,500 mg/m^2 at a rate of 10 mg/m^2/min on days 1, 8, and 15, every 28 days.

Table 1. Patient Characteristics

Characteristic	Gemcitabine/ Cisplatin (arm A)		FDR Gemcitabine (arm B)		Gemcitabine/ Docetaxel (arm C)		Gemcitabine/ Irinotecan (arm D)		All Patients	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Patients enrolled	66		64		65		64		259	
Patients treated	62		58		65		60		245	
Age, years										
Median	58.9		58.9		62.9		60.8		60.5	
Range	36-84		31-81		41-79		32-77		31-84	
Sex										
Male	35	56	38	66	40	62	41	68	154	63
Female	27	44	20	34	25	38	19	32	91	37
Performance status										
0	15	24	14	24	22	34	23	39	74	30
1	40	65	36	62	36	55	31	53	143	59
2	7	11	8	14	7	11	5	8	27	11
Prior treatment with FU										
No	58	94	49	84	58	89	51	86	216	89
Yes	4	6	9	16	7	11	8	14	28	11
Prior treatment with radiation therapy										
No	56	90	47	81	57	88	51	86	211	86
Yes	6	10	11	19	8	12	8	14	33	14
Median weeks on study treatment	9.6		6.1		8.4		12.1		9.0	
Required dose modifications or delays	58	94	45	78	46	71	49	83	198	81
Received second-line treatment after study	21	34	15	26	21	32	15	25	72	30

Abbreviations: FDR, fixed dose rate; FU, fluorouracil.

In arm C, gemcitabine was administered as a 30-minute infusion at a dose of 1,000 mg/m^2 on days 1 and 8, every 21 days. Docetaxel was administered immediately after gemcitabine at a dose of 40 mg/m^2 on days 1 and 8. Premedication with dexamethasone was recommended. In arm D, gemcitabine was administered as a 30-minute infusion at a dose of 1,000 mg/m^2 on days 1 and 8, every 21 days. Irinotecan was administered immediately after gemcitabine at a dose of 100 mg/m^2 on days 1 and 8.

A physical examination and an assessment of hematologic, hepatic, and renal function were carried out at baseline and on the first day of each subsequent cycle in all treatment arms. All patients had hematologic function measured again on day 1; patients in arm A (gemcitabine/cisplatin) or arm B (fixed dose rate gemcitabine) had hematologic function also measured on day 15. Renal function was repeated on day 15 for patients receiving gemcitabine/cisplatin. Dose reductions were instituted for febrile neutropenia, hematologic toxicity, pulmonary toxicity, neurotoxicity, or hepatic toxicity in all arms of the study. Drug-specific dose modifications were also instituted for renal toxicity (cisplatin), hypersensitivity reactions (docetaxel), or diarrhea (irinotecan). For other nonhematologic toxicities, treatment was held until resolution and then resumed at 75% of the previous dose of all drugs in the event of grade 2 or 3 toxicity or at 50% of the previous dose in the event of grade 4 toxicity.

Disease response was documented by computed tomography, which was performed at baseline and every two cycles for patients in arms A and B or every three cycles for patients in arms C and D. Tumor response was measured according to Response Evaluation Criteria in Solid Tumors (RECIST); however, given the extensive fibrosis common in primary pancreatic tumors, only metastatic tumor sites were considered measurable for response evaluation. Patients evaluable for CA 19-9 response included those whose baseline CA 19-9 was elevated $\geq$ 75% from normal. A CA 19-9 response was defined as a decrease of $\geq$ 75% sustained over two measurements at least 4 weeks apart. Patients continued treatment until documented disease progression, unacceptable toxicity, withdrawal of consent, or the investigator thought change in therapy was in the best interest of the patient.

Statistical Plan

OS at 6 months was the primary efficacy end point of the study and was measured from time of protocol registration to time of death from any cause. Assuming a median OS of 6 months, with 60 patients in each arm, the proportion of patients surviving 6 months could be estimated within, at most, $\pm$ 0.11 month with 90% confidence in each arm. Estimation of the biomarker CA 19-9 response was a secondary objective. Patients were additionally observed for radiologic tumor response, time to disease progression, and toxicity. Treatment arms were compared descriptively for efficacy and toxicity end points. OS and TTP were estimated using the Kaplan-Meier method. TTP was defined as the time from study entry until documented progression or death from pancreatic cancer. OS was measured from study entry until death from any cause.

RESULTS

Patient Characteristics

A total of 259 patients were enrolled onto the study between January 15, 2001 and December 12, 2003; the patient characteristics are listed in Table 1. Of the patients enrolled, 245 were eligible and received treatment. Patients were evenly distributed among the four treatment arms with regard to age and performance status. The majority of patients in all four arms (56% to 68%) were male. Less than 20% of patients in each arm had received prior adjuvant chemotherapy with fluorouracil or external-beam radiation. Thirty percent of patients subsequently received second-line chemotherapy after treatment on the study; the frequency of second-line therapy was similar in the four arms.

Table 2. Selected Grade 3 or 4 Adverse Events, According to Treatment Arm

	Maximum Toxicity Grade (% of patients)							
	Arm A: Gemcitabine/ Cisplatin (n = 62)		Arm B: FDR Gemcitabine (n = 58)		Arm C: Gemcitabine/ Docetaxel (n = 65)		Arm D: Gemcitabine/ Irinotecan (n = 60)	
Adverse Event	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Hematologic toxicity								
Neutrophils	27	19	26	22	18	14	18	7
Leukocytes	32	6	21	16	18	9	13	7
Platelets	47	2	22	3	9	0	12	2
Hemoglobin	13	3	12	0	14	2	5	0
Nonhematologic toxicity								
Fatigue	11	5	12	2	18	3	17	2
Hyperglycemia	6	3	7	2	32	2	8	2
Nausea	23	0	12	0	9	0	15	0
Vomiting	18	0	12	2	8	0	10	0
Dehydration	5	0	5	0	8	0	10	0
Diarrhea	0	0	2	0	6	2	18	0
Infection	6	0	4	2	13	0	3	0
Alkaline phosphatase	6	0	3	0	8	0	8	0
Anorexia	3	2	5	0	8	0	0	0
Dyspnea	0	0	2	0	9	0	3	2
Thrombosis	0	3	0	0	5	5	3	0
Bilirubin	2	0	2	2	2	0	3	0
Febrile neutropenia	2	0	3	0	5	0	2	0
Edema	3	0	2	0	2	0	3	2
GI bleeding	0	0	0	0	3	2	0	0

NOTE. Grade 3 or 4 adverse events experienced by two or more patients in any arm are listed. Grade 5 (fatal) toxicities included: arm A, renal failure (n = 2); arm B, infection (n = 1) and seizure (n = 1); and arm D, infection (n = 1).
Abbreviation: FDR, fixed dose rate.

Table 3. Reason for Treatment Discontinuation

Reason for Ending Treatment	Arm A: Gemcitabine/ Cisplatin (n = 62)		Arm B: FDR Gemcitabine (n = 58)		Arm C: Gemcitabine/ Docetaxel (n = 65)		Arm D: Gemcitabine/ Irinotecan (n = 60)		All Patients (N = 245)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Progressive disease	38	61	32	55	39	60	33	55	142	58
Adverse event	13	21	9	16	12	18	12	20	46	19
Death	3	5	6	10	7	11	5	8	21	9
Withdrew from study	7	11	9	16	7	11	6	10	29	12
Other	1	2	2	4	0		4	7	7	3

Abbreviation: FDR, fixed dose rate.

Study Treatment

The median length of time that patients remained on study treatment varied from 6.1 weeks (fixed dose rate gemcitabine) to 12.1 weeks (gemcitabine/irinotecan). Dose modifications or delays for toxicity were common and occurred in nearly all of the patients (94%) receiving gemcitabine/cisplatin, 83% of patients receiving gemcitabine/irinotecan, 78% of patients receiving fixed dose rate gemcitabine, and 71% of patients receiving gemcitabine/docetaxel.

Neutropenia was the most common significant hematologic toxicity, and fatigue was the most common nonhematologic toxicity; both occurred at a similar incidence in all four treatment arms (Table 2). Other toxicities seemed to be more treatment arm dependent and reflected known adverse effects of the regimens used. Thrombocytopenia, nausea, and vomiting were most pronounced in patients receiving gemcitabine/cisplatin, whereas diarrhea occurred almost exclusively in patients receiving gemcitabine/irinotecan. Grade 3 or 4 hyperglycemia developed in 34% of patients receiving gemcitabine and docetaxel and was likely related to pretreatment with corticosteroids.

Overall, 19% of the patients withdrew from the study as a result of adverse events; the rate of withdrawal as a result of adverse events was similar in the four treatment arms (Table 3). A total of 21 patients died while receiving study treatment. Of these, five patients were classified as having experienced grade 5 (fatal) toxicities. Two patients receiving gemcitabine/cisplatin died of treatment-induced renal failure. Two patients died of treatment-related infections (one receiving fixed dose rate gemcitabine and one receiving gemcitabine/irinotecan), and one patient receiving fixed dose rate gemcitabine experienced a fatal seizure.

Efficacy

Six-month survival, the primary end point, was similar in all four treatment arms and ranged from 53% (gemcitabine/cisplatin) to 57% (fixed dose rate gemcitabine and gemcitabine/irinotecan; Table 4). OS was also similar in all four treatment arms (Table 4; Fig 1A). The median OS ranged from 6.4 months (fixed dose rate gemcitabine) to 7.1 months (gemcitabine/irinotecan). The median TTP ranged from

Table 4. Efficacy Results According to Treatment Arm

Efficacy	Arm A: Gemcitabine/ Cisplatin (n = 56)		Arm B: FDR Gemcitabine (n = 43)		Arm C: Gemcitabine/ Docetaxel (n = 57)		Arm D: Gemcitabine/ Irinotecan (n = 51)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Radiologic response (RECIST)								
Complete response*	1	2	0		0		1	2
Partial response*	6	11	6	14	7	12	6	12
Stable disease	30	54	25	58	30	53	28	55
Progressive disease	19	34	12	28	20	35	16	31
CA 19-9 response	15/46†	33	16/38	42	19/48	42	16/48	33
Time to tumor progression, months								
Median	4.5		3.3		4.1		4.0	
95% CI	2.6 to 5.5		2.7 to 4.6		2.4 to 4.9		2.5 to 5.2	
Patients alive at 6 months	33	53	33	57	35	54	34	57
Overall survival, months								
Median	6.7		6.4		6.4		7.1	
95% CI	5.0 to 7.8		4.4 to 9.9		5.1 to 7.9		5.4 to 8.8	

Abbreviations: FDR, fixed dose rate; RECIST, Response Evaluation Criteria in Solid Tumors.
*Confirmed.
†No. of patients/total No. of patients.

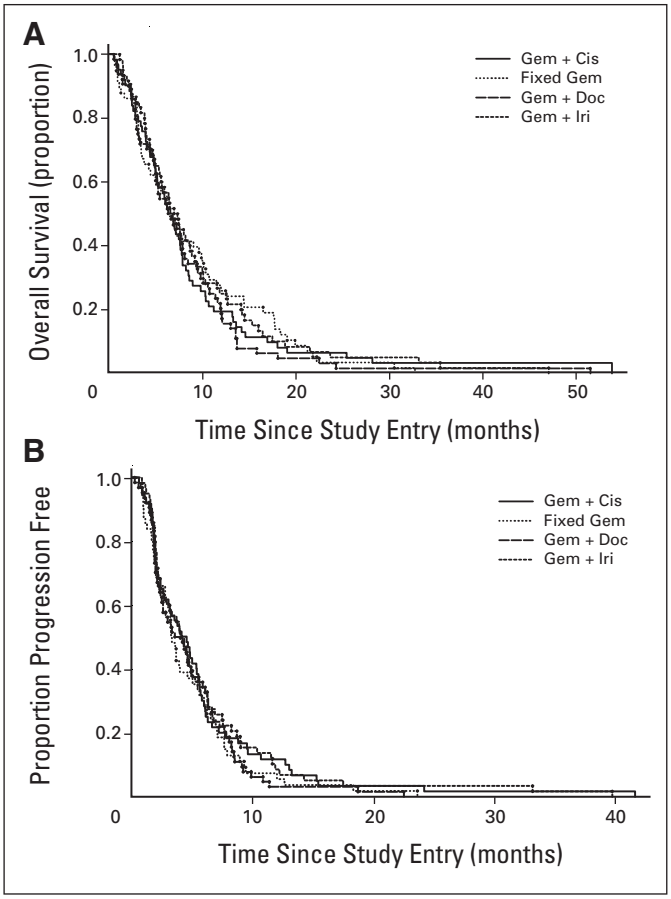

Fig 1. (A) Overall survival and (B) time to progression according to treatment arm. Gem, gemcitabine; Cis, cisplatin; Doc, docetaxel; Iri, irinotecan.

3.3 months (fixed dose rate gemcitabine) to 4.5 months (gemcitabine/cisplatin; Table 4; Fig 1B).

Radiologic and biochemical (CA 19-9) responses were secondary end points of our study. The number of patients evaluable for these end points was less than the number evaluable for survival as a result of the definitions of response used for the study (Table 4). One of the clinical characteristics of pancreatic cancer is extensive desmoplasia around the primary tumor, making it difficult to assess response or progression of disease at this site using standard imaging criteria. For the purposes of this study, therefore, we elected to consider only metastatic sites measurable for response. Confirmed radiologic response rates were indistinguishable among treatment arms and ranged from 12% (gemcitabine/docetaxel) to 14% (fixed dose rate gemcitabine and gemcitabine/irinotecan). CA 19-9 response rates were also similar between treatment arms and ranged from 33% (gemcitabine/cisplatin and gemcitabine/irinotecan) to 42% (fixed dose rate gemcitabine).

DISCUSSION

This multi-institutional, randomized, phase II study showed that four gemcitabine-based regimens (gemcitabine/cisplatin, fixed dose rate gemcitabine, gemcitabine/docetaxel, and gemcitabine/irinotecan) result in similar response and survival times in patients with advanced pancreatic cancer. Objective tumor response rates associated with the four regimens were within the narrow range of 12% to 14%. Median OS times were also similar and ranged from 6.4 to 7.1 months. Toxicities, although not prohibitive, were apparent in all four arms and were consistent with the anticipated effects of the four regimens. Consequently, we concluded that none of these regimens merited further assessment in a phase III study.

After the completion of this study, three of the four regimens we evaluated were directly compared with standard gemcitabine in randomized phase III trials performed by other groups. The combination of gemcitabine and cisplatin was evaluated in a German multicenter randomized trial comprising 195 patients, of whom 20% had locally advanced disease and 80% had metastatic disease.[14] The treatment regimen used in that study (cisplatin 50 mg/m^2 on days 1 and 15 and gemcitabine 1,000 mg/m^2 on days 1, 8, and 15 of a 28-day cycle) was identical to that used in our study. As in our study, nausea and vomiting, presumably secondary to the incorporation of cisplatin, were common. Tumor response rates were similar in the cisplatin/gemcitabine and gemcitabine alone arms (10.2% *v* 8.2%, respectively). Although both the reported progression-free and median survival times associated with the combination arm were longer than those associated with standard gemcitabine, the median survival difference did not reach statistical significance.

Fixed dose rate gemcitabine, which comprised the second arm of our study, was first compared with gemcitabine administered as a standard infusion in a randomized phase II study and, subsequently, with standard gemcitabine or fixed dose rate gemcitabine/oxaliplatin in an 833-patient, three-arm, randomized phase III study performed by the ECOG (ECOG 6201).[12,15] The randomized phase II study compared gemcitabine 1,500 mg/m^2 administered at a fixed dose rate of 10 mg/m^2/min (the regimen used in our study) with a standard 30-minute infusion of high-dose gemcitabine (2,200 mg/m^2).[12] The median survival time was 8 months in the fixed dose rate arm compared with only 5 months in the standard infusion arm ($P = .013$). In the subsequent phase III study (ECOG 6201), a small improvement in survival was observed with fixed dose rate gemcitabine, although this did not meet the threshold set for statistical significance.[15]

Two randomized trials have compared gemcitabine and irinotecan with standard gemcitabine. In the first study, which used the same gemcitabine/irinotecan regimen that was part of our study, the combination arm, compared with standard gemcitabine, was associated with a higher tumor response rate (16.1% *v* 4.4%, respectively) but no difference in OS (6.3 *v* 6.6 months, respectively).[16] The incidence of grade 3 or 4 diarrhea in patients receiving irinotecan in this study was 18.5%, which is identical to the 18% incidence observed in arm D of our study. A second randomized study comprising 145 patients used a different combination regimen, in which standard gemcitabine was compared with gemcitabine administered at a dose of 900 mg/m^2 weekly for 3 out of 4 weeks combined with irinotecan 300 mg/m^2 on day 8.[17] Combination therapy was again associated with a higher response rate compared with standard gemcitabine (15% *v* 10%, respectively), but there were no significant differences in TTP or median survival.

Survival durations associated with other combinations have also been either equivalent or only marginally superior to those associated with single-agent gemcitabine in randomized studies. The median survival time associated with gemcitabine/pemetrexed was 6.2 months, compared with 6.3 months with single-agent gemcitabine, in a randomized study comprising 565 patients.[18] A study performed by

the Groupe Cooperateur Multidisciplinaire en Oncologie (GERCOR) and Italian Group for the Study of Gastrointestinal Tract Cancer (GISCAD) compared standard gemcitabine with a regimen of fixed dose rate gemcitabine administered in combination with oxaliplatin.[19] This study reported an improvement in progression-free survival associated with the combination regimen but failed to demonstrate a significant OS difference.

One potential difficulty in comparing results across studies of novel regimens in pancreatic cancer has been the variable inclusion of patients with locally advanced and metastatic disease. To minimize patient heterogeneity in our study, we included only patients with metastatic disease. The median survival times associated with combination chemotherapy in our study, which ranged from 6.4 to 7.1 months, match closely with the median survival time reported for patients with metastatic disease receiving single-agent gemcitabine (6.7 months) in the GERCOR/GISCAD trial. This finding is consistent with our interpretation that none of the four regimens evaluated in our study is likely to offer a significant improvement over treatment with gemcitabine alone.

To date, only two gemcitabine-based regimens—gemcitabine/erlotinib and, in a preliminary report, gemcitabine/capecitabine—have been associated with statistically significant improvements in OS when compared directly with gemcitabine alone in the randomized setting.[3,4] In both of these two studies, the survival benefit was relatively small and was achieved at a cost of increased toxicity. Both the gemcitabine/capecitabine and gemcitabine/erlotinib randomized studies included more than 500 patients and were thus powered to detect small survival differences. Several meta-analyses have, in fact, suggested a benefit associated with combination chemotherapy.[20,21] The largest of these studies evaluated 9,970 patients from 51 randomized trials and reported a statistically significant survival advantage associated with gemcitabine combination therapy compared with gemcitabine alone (hazard ratio = 0.91; 95% CI, 0.85 to 0.97).[22] Whether this difference is clinically meaningful remains unclear, particularly in light of the enhanced toxicity associated with many combination regimens.

In conclusion, we observed similar efficacy associated with four gemcitabine-based regimens in patients with metastatic pancreatic adenocarcinoma. These findings do not support the further study of any of these regimens in this setting. Our study demonstrates the feasibility of evaluating four potentially promising regimens in a randomized fashion in this disease. The observed results are consistent with subsequent phase III studies in advanced pancreatic cancer and suggest that adopting a similar approach to evaluate future agents in pancreatic cancer may be an efficient way to rapidly assess which regimens to bring forward in phase III randomized studies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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