Gemcitabine and Capecitabine for Advanced Adenocarcinoma of the Pancreas

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Abstract

Background: Chemotherapy for advanced adenocarcinoma of the pancreas may have severe toxicities including neuropathy, leukopenia, and bleeding risks.

Methods: In a retrospective study, 79 patients with adenocarcinoma of the pancreas, TNM stage 3 or 4, or recurrent disease, received 2 or more cycles of monthly chemotherapy. Fifty-four patients had no prior chemotherapy, while 25 patients had progressed after chemotherapy. All patients were treated with monthly gemcitabine 3000 mg/m^2 by fixed-dose-rate infusion over 3 hours, and with capecitabine 14-day chemotherapy given at the highest dosage that was tolerated well. After escalation, capecitabine was stopped before 14 days if unusual toxicity was occurring. Patients with stage III disease received 2-5 cycles of chemotherapy preceding radiotherapy when radiotherapy was planned. Chemotherapy for nonresectable stage III or stage IV disease was continued if response was ongoing or improving, and was stopped when progressive disease was evident on radiological studies.

All statistics are presented as median +/- standard deviation and range.

Results: As determined by retrospective review, of those without prior chemotherapy, the median duration of progression-free survival was 8.1 +/- 7.9 months (range, 0-34.3 months). The median overall survival was 11.6 +/-9.1 months (range, 0.8-41.5 months). Four patients survived more than 3 years.

Conclusion: This monthly chemotherapy is well tolerated and provides an overall survival comparable to other intensive regimens. Further randomized phase 3 comparison trials are warranted.

Keywords: Advanced pancreatic cancer, gemcitabine, capecitabine.

Introduction

The current standard of chemotherapy for newly diagnosed patients with advanced pancreatic cancer is either FOLFIRINOX (5-fluorouracil [5-FU], leucovorin, irinotecan, and oxaliplatin) or gemcitabine/*nab*-paclitaxel regimens, but the 5-year survival rate is less than 5%. Conventional gemcitabine therapy requires weekly visits for patients, while the FOLFIRINOX regimen requires biweekly intravenous infusion therapy, and the gemcitabine/*nab*-paclitaxel regimen often causes progressive neuropathy, limiting the duration of therapy.

An alternative therapy has been developed that greatly improves the tolerability of chemotherapy, reduces the time burden on patients, and provides better tolerance of the treatment-induced side effects, and yet maintains duration of overall survival (OS). This therapy is fixed-dose-rate infusion of gemcitabine with capecitabine. This therapy was particularly well-tolerated relative to the rather toxic FOLFIRINOX therapy, and relative to the neuropathy common with gemcitabine/*nab*-paclitaxel regimens, especially in patients with impaired marrow tolerance due to prior radiotherapy, or with pre-existing neuropathy. A therapy of weekly gemcitabine and capecitabine was described by Knox et al[1] in the *Journal of Clinical Oncology* in 2005 for advanced biliary carcinomas, utilizing weekly gemcitabine on days 1 and 8, with capecitabine given at a dosage of 650 mg/m^2 twice daily for 14 days; cycles were repeated every 21 days. Prolonged fixed-dose-rate infusions were developed with the knowledge that phosphorylation of gemcitabine into the active gemcitabine triphosphate is catalyzed by deoxycytidine kinase, an enzyme that is saturated by 30 minutes. Therefore, enhanced antineoplastic activity requires prolonged infusion times; many physicians during the years 1999 to 2003 studied infusion times ranging from 30 minutes to 24 hours.[2-4] Prior studies with 5-FU and with fluorodeoxyuridine[5] demonstrated that individual dosage tolerances were extremely varied, suggesting that studies with dosage escalations according to individual patient tolerance were needed.

Capecitabine is an oral prodrug of 5-FU that is designed to exploit the differences in activating enzyme (thymidine phosphorylase) activity between tumor and normal tissue that results in a threefold increase in the concentration of the active metabolite in the tumor cell.[6] It was generally recognized that the useful chemotherapy drugs available are gemcitabine, 5-FU, oxaliplatin, bevacizumab, *nab*-paclitaxel, and recently the experimental nanosomal irinotecan MM-398. With few drugs available, the opportunities for development of combination chemotherapy are limited and cures are unlikely. Further development of new drugs for patients is anxiously awaited. **Table 1** shows the reported OS in the literature.

TABLE 1. Median OS Following Chemotherapy for Adenocarcinoma of the Pancreas

Regimen	Study Phase	N	Date	Median OS	Current Use
FDR Gem weekly[7]	2	40	2005	10 months	Occasional
FDR Gem weekly[8]	2	106	2006	7.3 months	Occasional
FOLFIRINOX every 2 weeks[9]	2-3	171	2011	11.1 months	Common
Gem-Ox every 2 weeks[10]	2	29	2010	15 months	Common
Gem-DDP[11]	2	51	2006	7 months	Common
Nab-paclitaxel + Gem[12]	1-2	431	2013	8.5 months	Common
Bev/Gem-Cap[13]	2	50	2009	9.8 months	Prior
CALGB 80803: Study of Gem weekly vs Gem-Bev[14]	3	535	2010	5.9 vs 5.8 months	Unusual

Cap indicates capecitabine; FDR, fixed-dose-rate; Gem, gemcitabine; Bev, bevacizumab; DDP, cisplatin; OS, overall survival; Ox, oxaliplatin.

With this background, we developed and piloted an alternative therapy, fixed-dose-rate infusion of gemcitabine with escalating-dose capecitabine, which has the potential to greatly improve tolerability and reduce the time burden on patients. We sought to examine whether this regimen could provide equivalent duration of OS as seen with other contemporary first-line regimens with less toxicity.

TABLE 2. Patient Characteristics

Characteristic	N
Under age 50 years	11
Prior radiotherapy	7
Progression After Prior Chemotherapy	**N**
No prior progression on chemotherapy	54
Progression on 1 regimen	21
Stage III	13
Stage IV	8
Progression on more than 1 regimen	4
ECOG Performance Status	**N**
0-2	78
>2	1
Distribution of Disease	**N**
Liver metastases	55
Lung metastases	22
Bone metastases	5
Good-risk disease (T4N1 disease)	14

METHODS

Patients

Our adult patients with stage IIB to IV pancreatic cancer included 54 patients with newly diagnosed advanced disease and 25 patients with prior chemotherapy and relapsed disease. These patients received treatment with a combination of gemcitabine and capecitabine. A retrospective case retrieval was used to analyze tumor response, OS, and treatment-related adverse events (AEs). We treated them from February 2008 to November 2013 at the Midwestern Regional Medical Center in Zion, Illinois.

Treatment-related toxicities were graded using the National Cancer Institute Common Toxicity Criteria, version 3 (2003).

Retrospective analysis was conducted after the Midwestern Institutional Review Board confirmed that the data collection was IRB-exempt, with all data collected being de-identified prior to analysis and reporting. As such, this study complied with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws.

Treatment Schedule

Each chemotherapy cycle consisted of every-4-week gemcitabine 3000 mg/m^2 by fixed-rate dose infusion over 3 hours. Capecitabine was dosed at a level tolerated by the patient, usually starting with the dosage of 2000 mg/m^2 twice daily for 14 consecutive days every month. Capecitabine dosage was increased to the highest dose tolerated with less than grade 3 toxicity. Frail patients received decreased dosage in the initial cycle, but escalation in the second cycle to customary doses. To minimize and control toxicities, each patient was instructed in supportive care, antidiarrhea care, and the particular steps needed for minimizing hand-foot syndrome.

Tumor Response

Monthly follow-up visits involved physical examination and standard laboratory tests including complete blood count (CBC), chemistries with liver function tests, and tumor markers. Radiographic studies were performed at 3-month intervals. Pain assessment was conducted using the visual analog scale to determine a decrease in pain levels of a tumor response.[15]

Statistical Methods

The primary end points of this retrospective study were evidence of tumor response, survival, time to progression, and the prevalence and grade of treatment-related toxicities. Survival was estimated using the Kaplan-Meier method. Survival was measured from the first cycle of therapy to patient death. The time to progression was measured from the first cycle until radiological evidence of more than 25% increase in the product of cross diameters of a measurable tumor site. Formal RECIST were not sought, as many patients had minimally measurable disease. Date of last follow-up was July 1, 2014. Living patients were censored to July 1, 2014.

RESULTS

Patient Demographics and Treatment History

Seventy-nine patients received therapy for stage IIB-III, recurrent disease, or stage IV pancreatic cancer (**Table 2**). These patients had a median age of 57.0 years (range, age 36-71 years), and 59% were male. Eighteen patients in this series had stage IIB-III cancer while 61 patients had stage IV disease. The median delay between the diagnosis and the onset of our therapy for the 43 previously untreated patients with stage IV disease was 1.6 +/- 2.5 months (range, 0-12.3 months), while the median delay for the 18 patients with prior chemotherapy was 7.7 +/- 7.5 months (range, of 0-29.8 months). Of the 25 patients with relapsed disease, 4 had progressed after more than 1 chemotherapy regimen and 7 had had prior radiotherapy.

TABLE 3. Median Survival: Subcategories of Patients With Stage III Disease

Category	N	Median Survial
Patients with mesenteric metastases who received gemcitabine-capecitabine as initial therapy	7	19.6 months
Received initial therapy with radiotherapy	3	24.3 months
Received other chemotherapy: FOLFIRINOX (1) Weekly gemcitabine (1)	2	Not applicable
Had laparotomy but was not resected	5	23.2 months
Laparotomy refused by the surgeon on a clinical basis	1	23.3 months
Resected after prior radiotherapy	4	21.9 months
Successful initial Whipple resection*	4	22.1 months

**No preceding chemotherapy.*

Treatment and Survival

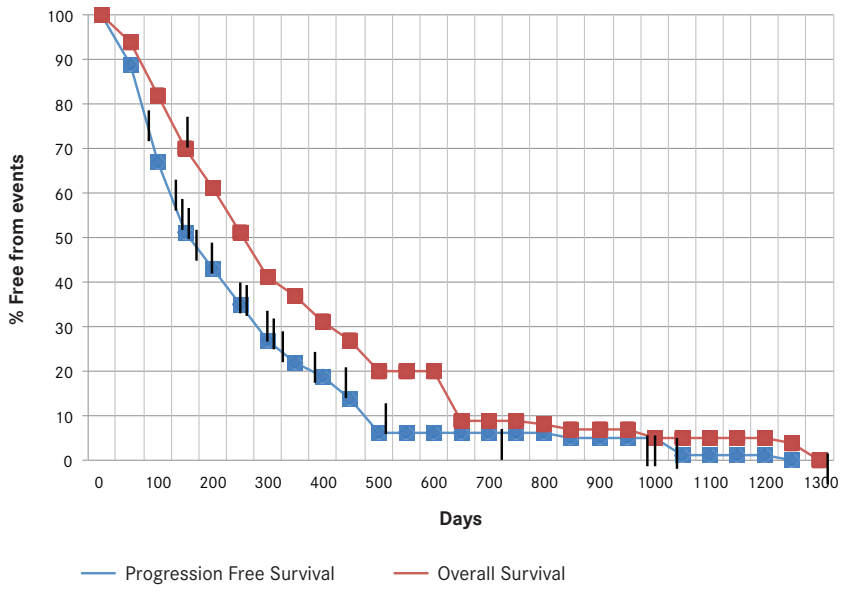
All patients analyzed for survival received at least 2 cycles of capecitabine unless severe toxicity was experienced in the initial cycle. Two patients who had previously received chemotherapy were lost to follow-up after 1 cycle of therapy and are not included in the results. All patients received gemcitabine 3000 mg/m^2 over 3 hours on the initial day of each monthly cycle. The highest dosage of capecitabine tolerated was 4 1/2 500-mg tablets twice daily for 14 days,with a standard deviation (SD) of 1.2 tablets twice daily, making a 95% confidence interval (CI) of 2 to 9 tablets twice daily times 14 days. The median number of treatment cycles was 7.2 (range, 2-41 cycles). Thirty-six patients had 6 or more cycles of therapy. As of July 2014, 12 patients were alive.

The median survival of all patients was 12.0 months (67% CI, 2.0-22.1 months; range, 0.8-44.8 months) with a 2-year survival of 9%. In the 53 newly diagnosed patients, the median survival was 11.6 months (67% CI, 2.5-20.7 months; range, 0.8-41.6 months) and a 2-year survival of 5%. The median survival of the patients who relapsed after gemcitabine-capecitabine was 3.6 months (67% CI,

TABLE 4. Median Duration of Survival in Various Groups

Patients	Median Survival (months)	Range	Number Alive as of 7-1-2014
Overall (n = 79)	12.0	0.8-44.8	12
Liver metastases (n=55)	8.2	0.8-44.4	6
No prior chemotherapy (n=54)	11.4	0.8-41.5	9
No prior chemotherapy (age>65) (n=4)	9.9	2.8-44.0	-
Prior radiotherapy (n=7)	19.6	1.8-44.0	-
No prior radiotherapy (n=72)	10.0	0.8-44.8	-
Stage IIB at baseline (n=1)	20.3	–	1
Stage III at baseline (n=17)	20.9	5.3-44.8	5
Stage III (nonresectable mesenteric disease) (n=7)	24	5.3-44.8	-
Stage IV at baseline (n=61)	9.4	0.8-44.0	6

FIGURE. Duration of Response and Overall Survival: All Patients



0.3-11.1 months). This is illustrated in the **Figure.**

The median survival of the 25 patients who had previously received chemotherapy was 13 months (67% CI, 1.0-24.9 months; range, 1.6-44.8 months). There was no statistically significant difference in these survival curves by the log rank test. Twelve patients had prior gemcitabine-containing therapy, often with radiotherapy, and their median survival was 15.2 months. The 14 patients with prior 5-FU-containing therapies had a median survival of 13.0 months, while the 7 patients with prior oxaliplatin-containing regimens had a median survival of 12.8 months. Median survival of patients with stage III disease is delineated in **Table 3**, and **Table 4** lists survival according to subgroups.

Four patients received only 1 cycle of therapy. The first patient had an ECOG performance status of 2 and massive ascites. The second patient had extensive liver metastases with an initial bilirubin of 3. The third patient had massive liver metastases with disease progression during the first cycle. The fourth patient apparently tolerated therapy well, but decided not to return for further chemotherapy for personal reasons.

Safety and Tolerability

Treatment-related AEs associated with this regimen included transient leukopenia generally lasting less than a week **(Table 5)**. There was universal alopecia, as well as 3 instances of grade 3 stomatitis, 2 instances of grade 3 hand-foot syndrome, and 1 instance of grade 3 leukopenia lasting longer than 7 days, but on no occasion was scheduled chemotherapy delayed due to toxicity. Capecitabine dosage was decreased in those with grade 3 stomatitis or hand-foot syndrome. Bone marrow support with granulocyte colony-stimulating factor was not routinely utilized.

Sixty-four patients had no nausea or vomiting, 68 had no stomatitis, and 48 had no hand-foot syndrome. Diarrhea was grade 2 in 7 patients and grade 3 in 2 patients. No patients experienced chemotherapy-induced thrombocytopenia. There were no grade 4 treatment-related toxicities. There was no therapy-related mortality (0 of 79 patients). Cholangitis and sepsis occurred in patients who had high-degree obstruction of the biliary ducts, occurring universally when leukopenia was absent. All deaths were a result of multiple organ failure due to the disease process. There was no imputation of results for the missing data.

Ten chemotherapy-naïve patients were initially treated with gemcitabine and capecitabine, and following progression received single-agent oxaliplatin at 120 mg/m^2 once monthly. Their average duration of freedom from progression to the initial gemcitabine phase was 7.5 months, and 5.5 months to the subsequent oxaliplatin. Median survival for patients in both phases

TABLE 5. Adverse Events

Regimen	None	Grade 1	Grade 2	Grade 3
Nausea/Vomiting	64	10	5	0
Stomatitis	68	3	5	3
Diarrhea	64	6	7	2
Hand-foot syndrome	48	25	4	2
Leukopenia lasting >7 days	74	2	2	1
Anemia	78	1	0	0
Alopecia	0	1	78	0
Thrombocytopenia	79	-	-	-
Patients requiring GCSF	77	2	-	-
Other adverse events: gout (1), antiplatelet antibodies (1), conjuctivitis, perleche (1), thrush (2).				

GCSF indicated granulocyte colony-stimulating factor.

was 13.3 months. This group included 1 patient whose response to the gemcitabine-capecitabine phase was 34.3 months, a prolonged survival 3 SD above the mean for the group. This patient was considered to be unusually responsive.

This study thus included 5 patients whose survival was longer than 2 SD above the mean of the other patients, suggesting they belonged to a subgroup, the basis of which will be studied in the future.

Conclusion

The chemotherapy regimen of fixed-infusion-rate gemcitabine- and escalting-dose capecitabine offers a well-tolerated regimen for patients utilizing a convenient monthly chemotherapy. This provides a significant increased quality of life for patients who need to receive chemotherapy. It provides comparable survival relative to more toxic contemporary regimens in patients and markedly prolonged survival in a subgroup of patients. This regimen merits a prospective trial, and ultimately should be compared with gemcitabine/*nab*-paclitaxel or FOLFIRINOX.

We are optimistic that genomic analysis of patients may provide a means to prospectively identify patients with pancreatic cancer whose biological subtype suggests the potential for prolonged survival. These studies are now in progress.

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