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ORIGINAL ARTICLE

The use of GTX as second-line and later chemotherapy for metastatic pancreatic cancer: a retrospective analysis

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Abstract
Purpose There are limited data regarding the role of second-line treatment for metastatic pancreatic cancer (mPC) after the failure of initial chemotherapy. No data exist on the use of GTX after the failure of first-line therapy.
Patients and methods We identified patients who were given GTX chemotherapy for a diagnosis of mPC after the failure of initial therapy. Demographic features, progression-free (PFS) and overall survival (OS), response to treatment, and toxicities were recorded.
Results The 59 evaluable patients received a median of 2 prior therapies. Three had no prior gemcitabine. Median PS was 1. Median survival was 22 weeks; progression-free survival was 9.9 weeks. Survival did not correlate with the number of prior regimens but trended with PS. There were no radiologic responses; those with stable disease ($n = 21$) had a better survival than those with progression ($n = 29$) or unevaluable patients ($n = 9$). Median survival was 38.3, 15.0, and 7.4 weeks, respectively. Grade 3 and 4 toxicities included leucopenia ($n = 14$), anemia ($n = 7$), and thrombocytopenia ($n = 6$). Hospitalizations were required in 21 patients, for febrile neutropenia ($n = 7$), non-neutropenic infection ($n = 3$), pulmonary embolus ($n = 2$), anemia or failure to thrive ($n = 9$). A 75% drop or more in CA 19-9 correlated with improved survival.
Conclusions GTX is an active regimen in patients previously treated with gemcitabine for mPC. Better performance status and >75% drop in pretreatment CA 19-9 were associated with longer survival. The number of prior regimens did not predict for survival duration.

Keywords Pancreatic cancer · Chemotherapy · Adenocarcinoma · Survival

Introduction

Pancreatic cancer is the fourth leading cause of cancer-related death in the United States, according to recent statistics [1]. The vast majority of patients initially present with locally advanced or metastatic disease, which is usually incurable. Systemic chemotherapy is the treatment of choice in this setting. In 1997, gemcitabine proved superior to 5-fluorouracil (5-FU) with respect to overall survival, reduction in symptoms, and tolerability of side effects and was widely adopted as the first-line treatment for pancreatic cancer [2]. However, the median survival time for patients with metastatic disease remains a paltry 6 months.

Attempts to improve on the results for gemcitabine have included the use of gemcitabine-based doublet and triplet chemotherapy regimens. Multiple agents have been tested in combination with gemcitabine, including cisplatin, oxaliplatin, irinotecan, and capecitabine [3–8]. Of these, only erlotinib has been demonstrated in a randomized trial to improve median survival—by 12 days [9].

Triplet regimens have shown promising signs of activity. In one recent study, patients with metastatic disease treated

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with Folfirinox (5-FU/leucovorin, irinotecan, and oxaliplatin) survived 10.6 months, as compared with 6.9 months among patients treated with gemcitabine alone [10]. The GTX regimen (gemcitabine, docetaxel, and capecitabine) also has shown promising activity. In a mixed cohort of patients, it resulted in an overall response rate of 29% and a median survival of 11.2 months [11].

As a result, GTX has become an often used chemotherapeutic regimen. However, there is a paucity of data evaluating the success of GTX as a second- or third-line therapy in patients with unresectable or metastatic pancreatic cancer. In order to describe the role of GTX in this setting, we conducted a retrospective evaluation of patients at MD Anderson Cancer Center treated with GTX as second-line or later therapy.

Methods

Patient selection

Permission for our work was first obtained from the MD Anderson Institutional Review Board, which waived the need for informed consent because of the retrospective nature of the study. We evaluated data for patients who were diagnosed with pancreatic adenocarcinoma between January 2001 and December 2009. From this group, we used pharmacy records to identify patients with pancreatic adenocarcinoma who received docetaxel as part of their chemotherapy treatment. Of those, we identified patients who received concurrent treatment with gemcitabine and capecitabine in the form of the GTX regimen. We then excluded patients who received GTX as first-line chemotherapy, and we excluded patients who received variations of the GTX regimen such as the inclusion of erlotinib or the substitution of infusional 5-FU for capecitabine. We did not exclude patients for adjustments in precise dosing of the three drugs.

Data for patients with various stages of disease, as well as post-surgical patients with metastases, were examined. Patients were not excluded based on the severity or stage of their disease. Patients who were lost to follow up or sought continued therapy at another institution besides MD Anderson were excluded if their records were unobtainable. Both patients with measurable disease and those with non-measurable disease were included in our study.

Patients whose treatment met these criteria were further evaluated with a chart review. Data such as comorbid conditions, baseline and nadir CA 19-9, previous therapies, and laboratory values were obtained.

Treatment regimen

The GTX regimen consisted of gemcitabine, docetaxel, and capecitabine. No other chemotherapeutic or radiologic treatment was administered during the course of GTX. In order for the patient to qualify for our analysis, each of these agents had to have been administered concurrently for the duration of their treatment cycle. The typical dosing pattern was consistent with those utilized in previous GTX studies [11]. Gemcitabine was typically given at a dose of 600 mg/m^2 over 60 min intravenously (IV), docetaxel was given at a dose of 30 mg/m^2 over 60 min (IV) on days 4 and 11 of the treatment cycle, and capecitabine was administered at 1000 mg/m^2/day divided into two doses given two times a day by mouth. Patients generally continued therapy until either disease progression or unacceptable toxicity occurred.

Assessment of performance

Radiologic response was defined by Response Evaluation Criteria in Solid Tumors (RECIST) for pancreatic cancer. Time to progression was defined as the duration from the first day of chemotherapy to the date of a CT scan documenting disease progression or death. Overall survival was defined as the duration from the first day of GTX chemotherapy to the date of death. Time to treatment failure was defined as the duration from the first date of chemotherapy to the date of discontinuation of chemotherapy for any cause.

Assessment of toxicity

Charts were retrospectively reviewed for toxicity data. Hematologic toxicity was assessed via available records. Non-hematologic toxicity was estimated from patient progress notes. The grades of the various toxic effects were assigned in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version 4 guidelines. Liver function abnormalities were graded; other non-hematologic toxicities were not graded as most did not have such non-hematologic toxicity prospectively graded. The presence of toxicities, when described, was recorded.

Statistical analysis

For the analysis of overall survival, Kaplan–Meier estimates were generated. Additionally, Kaplan–Meier estimates of overall survival stratified by CA 19-9 levels and disease status were included, along with *P* values based on the log-rank test. Progression-free survival and time to GTX failure were also estimated.

Results

We identified 59 patients with advanced pancreatic cancer refractory to at least one previous regimen of chemotherapy

Table 1 Patient demographics and clinical characteristics

Characteristics	Number (%)
Age	
Median	58.8
SD	9
Range	38–79
Sex	
Male	35 (59%)
Female	24 (41%)
Race/ethnicity	
White	48 (81.3%)
African American	2 (3.4%)
Latin	3 (5.1%)
Asian	4 (6.8%)
Middle Eastern	2 (3.4%)
Tumor stage on initial presentation	
I	0
II	1 (1.7%)
III	1 (1.7%)
IV	57 (96.6%)

who met our eligibility criteria. The baseline demographic information for our study group is listed in Table 1. The average age of the patients studied was 59 years (range: 38–79); 59% of the patients were men and 41% women. The most common ethnicity seen in our review was white, which comprised 81.3% of the total patients studied. Patients had initially presented with a variety of disease stages, though most had metastatic disease at the time of administration of GTX ($n = 57$, 96.6%).

Overall, the median number of prior chemotherapeutic regimens utilized was two (see Table 2). All but three of the patients analyzed had received prior gemcitabine-based therapy. The three patients who had not received gemcitabine had received 5-FU as their initial therapy. Median ECOG performance status for our study group was 1 (Table 2).

The median overall survival was 27 weeks (Fig. 1), and the median progression-free survival was 9.9 weeks (Fig. 2). Dates of death and progression were not available

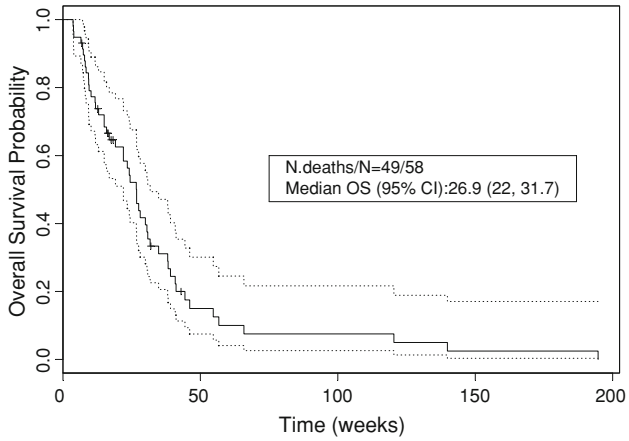

Fig. 1 Kaplan–Meier curve of overall median survival ($n = 58$)

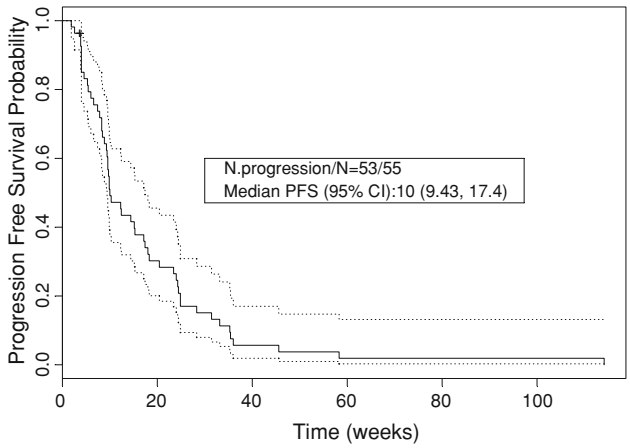

Fig. 2 Progression-free survival ($n = 55$)

for one and four patients, respectively. No demonstrable CT responses were seen in any of the patients studied. However, stable disease was observed in 21 patients (35.6%). Progressive disease during GTX treatment was seen in 29 patients (49.2%), and 9 patients were not evaluable by imaging (15.3%). Overall survival was significantly longer for patients who demonstrated disease stability as compared to those with progressive disease or those whose disease was unassessable (41, 19, and 9 weeks, respectively; Fig. 3; $P < .001$).

Table 2 Median overall survival by decrease in CA 19-9 level, ECOG performance status, and number of prior therapies

% Decline in CA 19-9	*N*	OS (weeks)	ECOG PS	*N*	OS (weeks)	No. Prior Rx	*N*	OS (weeks)
<0 (increase)	7	16.9	0	11	26.7	1	23	16
0–25%	4	27.6	1	22	22	2	13	11.9
26–50%	5	30.6	2	5	16.9	3	17	27.2
51–75%	7	32.4	3	2	5.9	4+	6	17.5
>75%	6	56.7	NR	19	23.2			

OS overall survival, *PS* performance status, *NR* not reported, *Rx* therapies

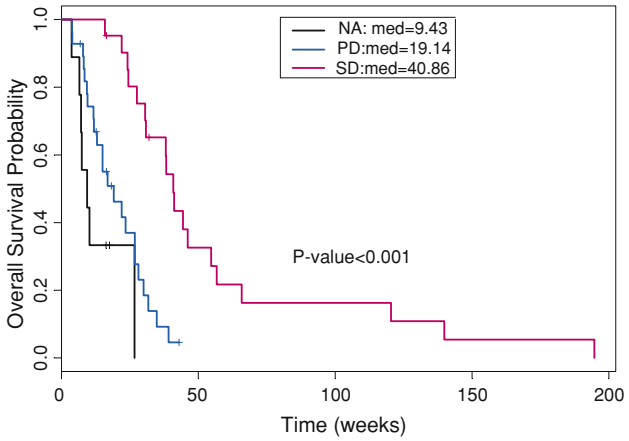

Fig. 3 Kaplan–Meier estimates for overall survival stratified by disease status ($n = 58$)

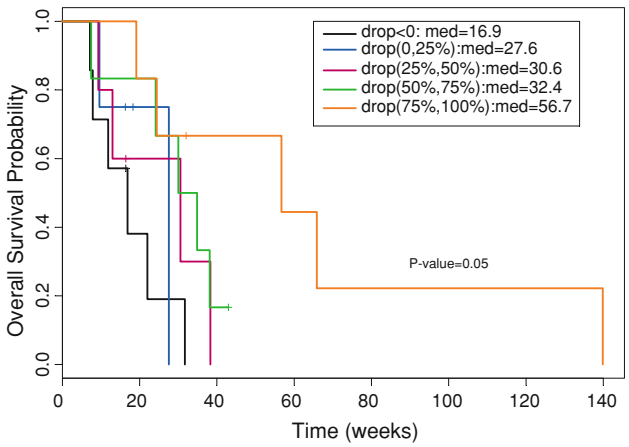

Fig. 4 Kaplan–Meier estimates for overall survival stratified by CA 19-9 drop ($n = 43$)

No association between overall survival and the number of prior regimens or baseline ECOG performance status was observed, though there was a trend favoring patients with better PS. Survival did correlate well with decrease in CA 19-9 level (Table 2; Fig. 4). Of the 29 patients with an initial CA 19-9 level >250 iU/ml, those exhibiting a 75% drop or more had the longest overall survival, with a median of 56.7 weeks on average.

Grade 3–4 hematologic toxic effects observed in our patients while on GTX included leukopenia ($n = 14$), anemia ($n = 7$), and thrombocytopenia ($n = 6$). In all, 16 patients (27%) had grade 3–4 hematologic toxicity. Liver function toxicity was mild—with grade 3 ALT elevation in 1 patient (2%) and grade 3 LDH elevation in 4 patients (8%). Twenty-one of the patients required hospitalization for febrile neutropenia ($n = 7$), non-neutropenic infections ($n = 3$), pulmonary emboli ($n = 2$), and anemia/failure to thrive ($n = 9$). Twenty-six (44%) of the patients went on to receive additional therapy after the conclusion of GTX.

Discussion

GTX is a regimen that has come into use for pancreatic cancer despite a paucity of formal phase II or phase III trial data. In retrospective analysis, median survival for patients who receive GTX as front-line therapy is roughly 11 months [11]. Our data suggest that there may be activity in the setting of second-line or later treatment. The 36% of patients who demonstrated stable disease did have a considerable overall survival duration of 41 weeks. Indeed, the median survival of 27 weeks for the entire group actually exceeds that of most phase II trials, an impressive figure considering the absence of radiologic response. Of note,

Table 3 Previously reported one, two, three, and four drug regimens for the second-line treatment of pancreatic cancer

Author	Year	Regimen	# Patients	Response	PFS (w)	OS (w)
Single drug						
Saif	2010	Docetaxel	17	6%	8	20
Two drugs						
Ko	2008	Docetaxel/irinotecan	14	0%	NR	19
Cereda	2010	FOLFIRI XELIRI	34	0	8	17
Yoo	2009	FOLFIRI	31	NR	8	17
You	2009	FOLFOX	30	7%	6	15
Gebbia	2007	FOLFOX	42	14%	16	27
Oh	2010	IROX	14	21%	6	16
Three drugs						
Dakik	2011	GTX	59	0	10	27
Reni	2004	MDI	15	0	7	24
Four drugs						
Reni	2008	PEFG*	46	24%	20	33

* Includes metastatic and locally advanced disease

however, this finding is after the selection for patients sufficiently strong for multiple lines of therapy, and it is not clear what percentage of patients with metastatic disease might be considered for GTX therapy.

Considering that the average patients received GTX as third-line therapy, a relatively low rate—27%—of patients experienced some grade 3–4 hematologic toxicity. There was little liver enzyme elevation. It is notable that only 12% of patients developed febrile neutropenia, considering the heavy load of prior therapies that patients received and the three-drug regimen employed.

The association of CA 19-9 decline with prolonged overall survival is not surprising. We chose to analyze only patients with a significantly elevated CA 19-9 level in order to exclude patients whose CA 19-9 level might have been influenced by prior biliary obstruction and to exclude patients whose tumors did not produce CA 19-9; their inclusion may have led to invalid results.

Currently, there is no standard of care for second-line therapy of pancreatic cancer, leaving oncologists to choose chemotherapeutic agents based on personal experience, anticipated side effects, and consideration of patient tolerance. These choices are often limited by the willingness of insurers to cover the costs of such treatment. Though polymorphism analysis [12] and expression of biomarkers such as ERCC1 [13] may emerge to guide therapy, such testing is not yet in routine clinical practice, and clinicians must rely on published data on available regimens to choose second-line (and later) regimens.

As second-line trials in pancreatic cancer are uncommon, much of such data will come in the form of retrospective evaluations, as we have done in our study. Unfortunately, many of these reports will contain only small numbers of patients.

Previous retrospective studies of chemotherapy for second-line pancreatic cancer include the results for single agents such as docetaxel [14]; doublets such as irinotecan with docetaxel [15], IROX [16], FOLFOX [17], and FOLFIRI [18, 19]; triplets such as MDI [20]; and even the quadruplet regimen PEFG [21] (see Table 3). These studies have generally offered progression-free survival times of 8–16 weeks and survival of approximately 15–20 weeks. While we do not advocate a direct comparison of GTX with the other regimens based on the earlier publications, our results compare favorably with these earlier studies.

Our results compare particularly favorably considering that our patients generally received GTX as a third-line regimen. It is important to consider that our analysis made no discriminations based on the number of prior regimens, and for several of the patients studied, more than 4 previous regimens had failed. Indeed, the number of previous regimens did not significantly correlate with survival in our analysis. However, it becomes difficult to determine the extent of the toxic effects observed in these patients that were a result of GTX specifically, rather than of the cumulative effects of long-term chemotherapy, such as bone marrow exhaustion. The greatest limitations of the GTX regimen in the treatment of patients with refractory disease were hematologic toxic effects.

Conclusion

The results of our analysis demonstrate that GTX appears to be an active regimen in patients with metastatic pancreatic cancer in which previous treatment with a gemcitabine-based regimen has failed. Though limited by significant toxic effects, there was a noteworthy survival benefit for patients treated with GTX in the setting of second-line and later therapy in our study. Overall survival, progression-free survival, and the percentages of patients with stable disease were similar to those reported for other recently published doublet or triplet chemotherapy regimens used in comparable patient populations.

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