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A two-cohort phase 1 study of weekly oxaliplatin and gemcitabine, then oxaliplatin, gemcitabine and erlotinib during radiotherapy for unresectable pancreatic carcinoma

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Abstract

Objectives—Gemcitabine is a potent radiosensitizer. When combined with standard radiotherapy (XRT) the gemcitabine dose must be reduced to about 10% of its conventional dose. Oxaliplatin and erlotinib also have radiosensitizing properties. *In vitro*, oxaliplatin and gemcitabine have demonstrated synergy. We aimed to determine the maximum tolerated dose of oxaliplatin and gemcitabine with concurrent XRT, then oxaliplatin, gemcitaibine and erlotinib with XRT in the treatment of locally advanced and low volume metastatic pancreatic or biliary cancer.

Methods—A modified 3 + 3 dose escalation design was employed testing 4 dose levels of oxaliplatin and gemcitabine given once weekly for a maximum of 6 weeks with daily XRT in fractions of 1.8 Gy to a total dose of 50.4 Gy. Dose limiting toxicity (DLT) was defined as any grade 4 toxicity or grade 3 toxicity resulting in treatment delay greater than one week. Additionally, dose reduction in two of three patients in a given cohort was counted as a DLT in dose escalation-deescalation rule in the modified 3 + 3 design.

Results—Eighteen patients were enrolled, all with pancreatic cancer. Grade 4 transaminitis in a patient in cohort 3 resulted in cohort expansion. Cohort 4, the highest planned dose cohort, had no DLTs. The recommended phase II dose (RPTD) is oxaliplatin 50 mg/m^2/wk with gemcitabine 200 mg/m^2/wk and 50.4 Gy XRT The most prevalent grade 3 toxicities were nausea (22%), elevated transaminases (17%), leucopenia (17%) and hyperglycemia (17%). Median progression free survival was 7.1 months (95% CI, 4.6–11.1 months) and median overall survival was 10.8 months (95% CI, 7.1–16.7 months). The addition of erlotinib was poorly tolerated at the first planned dose level, but full study of the combination was hindered by early closure of the study.

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Conclusions—Weekly oxaliplatin 50 mg/m^2/wk combined with gemcitabine 200 mg/m^2/wk and XRT for pancreatic cancer has acceptable toxicity and interesting activity.

Introduction

A significant fraction of patients with pancreatic cancer have unresectable locally advanced disease at diagnosis with a median overall survival (OS) in the range of 9 to 12 months[1]. Despite assiduous research, there has been relatively little advancement in the treatment of locally advanced pancreatic cancer. Recently there has been significant debate about the relative effectiveness of chemoradiotherapy versus chemotherapy alone[2]. However, the consequences of failure to control local disease should not be underestimated; uncontrolled primary disease has been associated with pain, nausea, vomiting, weight loss, obstruction and decreased survival [3].

A number of studies have investigated chemoradiotherapy in locally advanced pancreatic cancer. Cancer and Leukemia Group B conducted a phase II trial of low-dose twice weekly gemcitabine (60mg/m2) and concurrent radiation (XRT, 50.4 Gy) with considerable toxicity and a median OS of 8.2 months.[4] There has been similar toxicity in other phase II trials using higher doses of gemcitabine administered once or twice weekly with relatively small radiation fields. As an example, a European phase II study tested weekly gemcitabine (100 mg/m^2 as a continuous infusion over 24 hours) plus concurrent XRT (50.4 Gy), followed by five cycles of standard-dose gemcitabine, in patients with locally advanced pancreatic cancer. Grade 3/4 toxicity was observed in half the patients, but the median OS was 15.5 months and 25% of patients were alive at two years[5]

Oxaliplatin has synergistic cytotoxicity when combined with gemcitabine in human cancer cell lines *in vitro* or in xenografts. [6] Several clinical trials have demonstrated the efficacy of oxaliplatin and gemcitabine in various solid tumors, including pancreatic cancer, with response rates ranging from 10 to 30%, but no improvement in OS has been demonstrated [7–9]. Two recent phase 1 clinical trials in pancreatic cancer demonstrated the feasibility of combining oxaliplatin and gemcitabine with concurrent XRT encompassing narrower radiation fields [10, 11].

Our aim was to define the safety and tolerability of gemcitabine and oxaliplatin given on a once weekly schedule with full doses of XRT for maximum local control, in the treatment of locally advanced and/or low volume metastatic pancreatic cancer. A second phase of the study, which added erlotinib to the combination, was initiated but not completed due to termination of funding; results for the patients enrolled in that substudy are also presented.

Methods

Patients

The study (National Clinical Trials Number, NCT00266097, local IRB# 04-MED-294-ORC) was performed at two academic centers. Eligible patients had biopsy proven unresectable locally advanced or metastatic (at the discretion of the treating team) pancreatic carcinoma, ECOG performance status 0–2, a life expectancy greater than 2 months, adequate hematologic, renal and hepatic function, and a washout period of at least 3 weeks after previous anticancer therapy. During the second phase of the study (erlotinib phase), patients taking strong inducers or inhibitors of CYP3A were required to stop the medication to enter the study. The human subjects committees at each participating center approved this study and all patients provided written informed consent prior to participation. All trial procedures were conducted in accordance with the principles established by the Helsinki Declaration.

Study design

In the first part of the study, doses of gemcitabine and oxaliplatin were escalated using a modified 3 + 3 dose escalation design (Table 1). The second portion of the study added erlotinib (administered daily beginning on day1) p to the doses of gemcitabine and oxaliplatin that were one level below the recommended phase II dosing determined in the first part of the study. Gemcitabine was administered over 30 minutes and oxaliplatin was administered over 2 hours weekly during radiotherapy. Dose-limiting toxicity (DLT) was defined as any grade 4 toxicity, or grade 3 toxicity causing a delay in treatment for more than a week. Additionally, a dose level was deemed to be too toxic if dose reductions were required for two of three patients in a given cohort. This modification of the standard 3 + 3 dose escalation-de-escalation design prevents selection of a recommended phase II dose (RPTD) with a high rate of dose reductions. A dose level with 6 patients treated was considered intolerable if two occurrences of DLT were observed, or at least one DLT and dose reduction in at least 2 patients with the prior level declared the maximum tolerated dose (MTD). Gemcitabine and oxaliplatin dose reduction was allowed, with 20% dose reduction for grade 3 and 40% reduction for grade 4 toxicity. All agents were held if radiotherapy was held for toxicity. Additionally, all therapy was held for weight loss of 15% or more.

Radiotherapy was administered in fractions of 1.8 Gy to a total dose of 50.4 Gy using conformal planning and a multi-field technique. Gross tumor volume (GTV) was defined as the tumor as visualized on CT or MRI or as defined by operative findings including the pancreatic mass and any lymph nodes measuring more than 1.5 cm. Clinical target volume (CTV) was defined by expanding the GTV by 1 to 1.5 cm in directions for which there is no anatomic barrier to microscopic spread. An additional margin of at least 1.0 cm was added to the CTV for set up error and patient movement.

Safety evaluations were made at baseline and at weekly visits and included history and physical examinations, laboratory panels, and measurements of CA 19-9 at the outset and at the end of XRT. Response assessment by CT or MRI was done one month after completion of study therapy according to the Response Evaluation Criteria in Solid Tumors (RECIST v1.0). Adverse events were scored according to the National Cancer Institute Common Terminology Criteria of Adverse Events (CTCAE v3.0)

Descriptive analyses were performed for all the demographic and analytic data. Categorical data were summarized using frequency tables and summary statistics such as mean, median, standard deviation, and range were obtained for continuous data. Survival was analyzed using the Kaplan-Meier statistic.

Results

A total of 18 patients were treated on this protocol (Table 2). All had pancreatic cancer. The median age was 60. Four patients had chemotherapy prior to study treatment. Most of the tumors were in the head of the pancreas. One patient had low-volume metastatic disease that had progressed on gemcitabine-based chemotherapy.

Table 3 describes grade 3 and 4 toxicities. One DLT (grade 4 elevated AST without evidence of cholangitis) occurred in a patient at dose level 3 and a dose reduction occurred in one patient. This dose level was expanded to 6 patients and no other patients experienced a DLT or dose reduction. One patient experienced a DLT and one patient a dose reduction at dose level 4, the highest dose level evaluated. After expansion of this dose level, the erlotinib study began, as described below.

Common grade 1 and 2 toxicities were nausea, vomiting, diarrhea, weight loss, thrombocytopenia and leukopenia. The most commonly encountered grade 3 toxicities were nausea (22%), elevated transaminases (17%), leucopenia (17%) and hyperglycemia (17%). Treatment delays and subsequent dose reductions occurred at dose level 1 (n=1), dose level 2 (n=2), dose level 3 (n=2 of 6, one of which was a DLT) and dose level 4. The highest tested combination was gemcitabine 200 mg/m^2 weekly, oxaliplatin 50 mg/m^2 weekly and XRT 50.4 Gy over 5 to 6 weeks, which produced manageable toxicity and represents the dose we would recommend for further evaluation.

All 18 patients completed XRT and each was evaluable for response assessment. Responses included one partial response, one complete response, and 14 (78%) with stable disease. Only 2 patients experienced progression at their first evaluation. Median progression free survival was 7.1 months (95% CI, 4.6–11.1 months) and median OS was 10.8 months (95% CI, 7.1–16.7 months).

Five patients were treated in Part 2 of the study, in which erlotinib was added to gemcitabine and oxaliplatin (Table 1). At dose level 1, two DLTs occurred. One patient was hospitalized for nausea, vomiting and diarrhea and another missed more than a week of treatment due to weight loss and cytopenias. This prompted de-escalation to dose level -1. Accrual was slow, however, and the study was closed early because the sponsors withdrew funding. Grade 3 toxicities in the limited number of patients treated included cytopenias, nausea, vomiting, diarrhea and anorexia.

Discussion

There is a persistent controversy over how best to treat locally advanced and metastatic pancreatic cancer and little convincing evidence to recommend any ‘new’ therapy since gemcitabine was approved in the 1990s. However, a strong rationale remains for studying new chemoradiotherapy regimens. Localized disease may profoundly affect quality of life and control of local disease may help palliate some of the most agonizing symptoms of pancreatic cancer-- pain, obstruction and cachexia. Radiotherapy, using chemosensitizing agents, may have an important role in the management of local disease. Gemcitabine acts as a radiosensitizer when combined with standard XRT, however gemcitabine doses must be reduced by approximately 10 to 30% of conventional doses, delivering suboptimal systemic drug concentrations[1]. Oxaliplatin also has radiosensitizing properties, and combinations of oxaliplatin and gemcitabine have demonstrated synergy in various studies. Combining the two agents in the locally advanced setting may improve systemic effect, and at the same time provide local control. We were able to demonstrate that full dose XRT can be integrated safely into this combination regimen. The highest tested combination was gemcitabine 200 mg/m^2 and oxaliplatin 50 mg/m^2 weekly with 50.4 Gy XRT over 5 to 6 weeks, which produced manageable toxicity.

Two other recent phase I/II trials have investigated the feasibility of using oxaliplatin and gemcitabine and concurrent XRT in the treatment of pancreatic cancer. One group of investigators administered oxalipatin (escalated to 85 mg/m^2), full dose gemcitabine and an attenuated XRT dose. Grade 3 and 4 toxicities included thrombocytopenia, worsening of performance status, GI bleed, and other GI toxicities[10]. Another group administered two cycles of gemcitabine and oxaliplatin followed by escalating weekly doses of oxaliplatin (up to 70 mg/m^2), a fixed dose of gemcitabine (300 mg/m^2) and radiotherapy to 45 Gy (for a total of 5 weeks) with acceptable toxicity[11]. Median time to progression was 8 months and OS was 17 months

In our study, oxaliplatin and gemcitabine were also combined at less than standard doses but with a conventional dose of radiotherapy. There was no major toxicity at the highest planned

doses of the two agents. PFS and OS in this study compares favorably to the survival results found in the Laurent study [11], which was very similar in design. Recent data from a chemotherapy-first approach in locally advanced pancreatic cancer[12] suggest that perhaps a strategy of chemotherapy alone followed by chemoradiation for patients who do not progress systemically is an approach with the best tradeoff between efficacy and minimization of toxicity. A gemcitabine/oxaliplatin/radiotherapy combination would be worth exploring within such a trial.

Our experience with erlotinib was limited by trial closure, but was associated with significant toxicity at the first planned dose level. Others have had experience with erlotinib plus radiotherapy combinations in pancreatic cancer. Iannitti et al utilized a regimen of gemcitabine (75 mg/m2 weekly), paclitaxel (40 mg/m2 weekly) and erlotinib, with the finding that erlotinib MTD was 50 mg daily [13]. Using a lower dose of gemcitabine of 40 mg/m2 twice weekly, Duffy et al. found the MTD of erlotinib to be 100 mg daily with hematologic toxicities comprising the DLTs. OS in that study was particularly interesting at 18.7 mos [14]. Tempering our enthusiasm for further study, however, is the recent experience in rectal cancer, where the addition of oxaliplatin to 5-FU based chemoradiation has produced disappointing results [15].

In summary, gemcitabine (200 mg/m2 weekly) and oxaliplatin (60 mg/m weekly) can be combined with standard-dose RT (1.8 Gy fractions to 5040 Gy). Lower doses of chemotherapy are required if erlotinib is added, even at only 50 mg daily. OS results in this study were promising, although the group was somewhat heterogeneous and the sample size small, tempering our enthusiasm to recommend this regimen for further study.

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References

1. Russo S, Butler J, Ove R, Blackstock AW. Locally advanced pancreatic cancer: a review. Semin Oncol. 2007; 34(4):327–334. [PubMed: 17674961]
2. Philip PA, Mooney M, Jaffe D, Eckhardt G, Moore M, Meropol N, Emens L, O'Reilly E, Korc M, Ellis L, et al. Consensus report of the national cancer institute clinical trials planning meeting on pancreas cancer treatment. J Clin Oncol. 2009; 27(33):5660–5669. [PubMed: 19858397]
3. Murphy JD, Adusumilli S, Griffith KA, Ray ME, Zalupski MM, Lawrence TS, Ben-Josef E. Full-dose gemcitabine and concurrent radiotherapy for unresectable pancreatic cancer. Int J Radiat Oncol Biol Phys. 2007; 68(3):801–808. [PubMed: 17379445]
4. Blackstock AW, Tepper JE, Niedwiecki D, Hollis DR, Mayer RJ, Tempero MA. Cancer and leukemia group B (CALGB) 89805: phase II chemoradiation trial using gemcitabine in patients with locoregional adenocarcinoma of the pancreas. Int J Gastrointest Cancer. 2003; 34(2–3):107–116. [PubMed: 15361643]
5. Mattiucci GC, Morganti AG, Valentini V, Ippolito E, Alfieri S, Antinori A, Crucitti A, D'Agostino GR, Di Lullo L, Luzi S, et al. External beam radiotherapy plus 24-hour continuous infusion of gemcitabine in unresectable pancreatic carcinoma: long-term results of a phase II study. Int J Radiat Oncol Biol Phys. 76(3):831–838. [PubMed: 19427747]
6. Moschidis A, Papageorgiou A, Atmatzidis K, Tsalis K, Moschidis E, Livanis J, Chrysogelou E, Mourelatos D, Tsavdaridis D, Harlaftis N. Synergistic antitumor activity of oxaliplatin in combination with gemcitabine in pancreatic tumor-bearing mice. Chemotherapy. 2007; 53(3):153–159. [PubMed: 17347561]
7. Alberts SR, Townley PM, Goldberg RM, Cha SS, Sargent DJ, Moore DF, Krook JE, Pitot HC, Fitch TR, Wiesenfeld M, et al. Gemcitabine and oxaliplatin for metastatic pancreatic adenocarcinoma: a

North Central Cancer Treatment Group phase II study. Ann Oncol. 2003; 14(4):580–585. [PubMed: 12649105]

8. Louvet C, Andre T, Lledo G, Hammel P, Bleiberg H, Bouleuc C, Gamelin E, Flesch M, Cvitkovic E, de Gramont A. Gemcitabine combined with oxaliplatin in advanced pancreatic adenocarcinoma: final results of a GERCOR multicenter phase II study. J Clin Oncol. 2002; 20(6):1512–1518. [PubMed: 11896099]
9. Mavroudis D, Pappas P, Kouroussis C, Kakolyris S, Agelaki S, Kalbakis K, Androulakis N, Souglakos J, Vardakis N, Nikolaidou M, et al. A dose-escalation and pharmacokinetic study of gemcitabine and oxaliplatin in patients with advanced solid tumors. Ann Oncol. 2003; 14(2):304–312. [PubMed: 12562660]
10. Desai SP, Ben-Josef E, Normolle DP, Francis IR, Greenson JK, Simeone DM, Chang AE, Colletti LM, Lawrence TS, Zalupski MM. Phase I study of oxaliplatin, full-dose gemcitabine, and concurrent radiation therapy in pancreatic cancer. J Clin Oncol. 2007; 25(29):4587–4592. [PubMed: 17925553]
11. Laurent S, Monsaert E, Boterberg T, Demols A, Borbath I, Polus M, Hendlisz A, de Hemptinne B, Mahin C, Scalliet P, et al. Feasibility of radiotherapy with concomitant gemcitabine and oxaliplatin in locally advanced pancreatic cancer and distal cholangiocarcinoma: a prospective dose finding phase I–II study. Ann Oncol. 2009; 20(8):1369–1374. [PubMed: 19457936]
12. Ko AH, Dito E, Schillinger B, Venook AP, Bergsland EK, Tempero MA. Phase II study of fixed dose rate gemcitabine with cisplatin for metastatic adenocarcinoma of the pancreas. J Clin Oncol. 2006; 24(3):379–385. [PubMed: 16344320]
13. Iannitti D, Dipetrillo T, Akerman P, Barnett JM, Maia-Acuna C, Cruff D, Miner T, Martel D, Cioffi W, Remis M, Kennedy T, Safran H. Erlotinib and chemoradiation followed by maintenance erlotinib for locally advanced pancreatic cancer: a phase I study. Am J Clin Oncol. 2005 Dec; 28(6):570–575. [PubMed: 16317266]
14. Duffy A, Kortmansky J, Schwartz GK, Capanu M, Puleio S, Minsky B, Saltz L, Kelsen DP, O'Reilly EM. A phase I study of erlotinib in combination with gemcitabine and radiation in locally advanced, non-operable pancreatic adenocarcinoma. Ann Oncol. 2008 Jan; 19(1):86–91. Epub 2007 Sep 17. [PubMed: 17878176]
15. Gérard JP, Azria D, Gourgou-Bourgade S, Martel-Laffay I, Hennequin C, Etienne PL, Vendrely V, François E, de La Roche G, Bouché O, Mirabel X, Denis B, Mineur L, Berdah JF, Mahé MA, Bécouarn Y, Dupuis O, Lledo G, Montoto-Grillot C, Conroy T. Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodige 2. J Clin Oncol. 2010 Apr 1; 28(10):1638–1644. Epub 2010 Mar 1. [PubMed: 20194850]

Table 1

Dose escalation Schema (note all patients received RT to 50.4 Gy)

Part 1	Oxaliplatin	Gemcitabine
Cohort -1	30mg/m^2/wk	60mg/m^2/wk
Cohort 1	30mg/m^2/wk	100mg/m^2/wk
Cohort 2	30mg/m^2/wk	200mg/m^2/wk
Cohort 3	45mg/m^2/wk	200mg/m^2/wk
Cohort 4	50mg/m^2/wk	200mg/m^2/wk

Part 2	Oxaliplatin	Gemcitabine	Erlotinib
Cohort -1	30 mg/m^2/wk	60mg/m^2	50mg daily
Cohort 1	45 mg/m^2/wk	100mg/m^2	50mg daily

Table 2

Demographic data

Median Age (range), years	59.5 (47–79)
Gender, n (%)	
Female	10 (56)
Male	8 (44)
Race, n (%)	
White	14 (78)
Black	4 (22)
Disease site (%)	
Head of pancreas	12 (67)
Body of pancreas	4 (28)
Overlapping lesion of pancreas	1 (5)
Prior chemotherapy, n (%)	
Yes	2 (11)
No	16 (89)

Table 3

Number of Participants with Drug-Related Grade 3 and 4 Toxicities by Cohort

	Cohort 1 (n=3)		Cohort 2 (n=3)		Cohort 3 (n=6)		Cohort 4 (n=6)	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Elevated transaminases	2					1*		
Leukopenia			1		2			
Hyperglycemia					2		1	
Nausea	2				2			
Vomiting	1				1			
Hyponatremia							2	
Fatigue					2			
Dehydration	1		1					

*Dose-limiting toxicity

Table 4

Stage, prior therapy and treatment outcome for all patients

Pt		Stage	Size	Prior Gem[1]	G/O/E doses	DLT?	Response	Site	Surg (R0)	OS
1	WD	T4N0M0	3.9 cm	Y	100/30/0	N	SD 6 mos[2]	L	N	7.5 mos
2	CD	T4N0M0	4.4 cm	N	100/30/0	N	SD 3 mos	D	N	5 mos
3	TF	T4N0M0	4.0 cm	N	100/30/0	N	SD 5.5 mos	U	N	12 mos
4	RS	T3N0M0[3]	3.5 cm	N	200/30/0	N	MR 3 mos	NA[4]	Y	3 mos
5	JR	T4N0M0	3.7 cm	N	200/30/0	N	PR 11 mos	D	N	40 mos
6	AG	T4N0M0	4.0 cm	N	200/30/0	N	SD 5 mos	L	N	9 mos
7	DM-W	T4N0M0	2.8 cm	Y	200/45/0	Y	SD 11 mos	L/D	N	17 mos
8	MF	T4N0M0	3.1 cm	N	200/45/0	N	PD	L	N	14.5 mos
9	MD-W	T4N0M0	4.8 cm	N	200/45/0	N	PD	L/D	N	7.5 mos
10	AT	TXN1M1[5]	2.5 cm	N	200/45/0	N	NA	D	N	11 mos
11	DB-W	T3N0M0	3.1 cm	N	200/45/0	N	PR	NA	Y	> 24 mos[6]
12	VSM	T4N1M0	5.0 cm	N	200/45/0	N	SD 15 mos	D	N	24 mos
13	OG	T4N0M0	2.5 cm	N	200/60/0	N	SD 14 mos	D	N	18 mos
14	JS	T4N0M0	3.5 cm	N	200/60/0	N	PD	D	N	3 mos
15	PD	T4N0M0	5.6 cm	N	200/60/0	N	PD	D	N	7 mos
21	MH	T3N1M0	2.5 cm	N	200/60/0	Y	PD	L	N	11 mos
22	GF	T4N1M0	3.1 cm	N	200/60/0	N	SD 3 mos	L	N	13 mos
23	LR	T4N0M0	NM	N	200/60/0	N	SD 4 mos	U	N	4 mos
16	DB	T4N0M0	4.8 cm	Y	100/45/50	N	SD 15 mos	L/D	N	18 mos
17	BLV	T4N1M0	3.3 cm	Y	100/45/50	Y	PD	L	N	4 mos
18	FB	T4N0M0	4.4 cm	N	100/45/50	Y	SD (unk)	U	N	10 mos
19	DT	T4N0M0	NM	Y	60/45/50	N	PD	D	N	6 mos
20	JS	T4N0M0	3.3 cm	N	60/45/50	N	Unkown	U	N	12 mos

[1] Not all patients failed gemcitabine, some had chemotherapy while awaiting a spot on trial

[2] At last available follow-up imaging

[3] Possibly ampullary tumor, although pathology not definitive for panc head vs. ampulla

[4] Died of sepsis post-op, R0 resection

[5] Two 1cm liver metastases

[6] Alive as of end of follow-up without recurrence after surgical resection

Abbreviations:
G/O/E-gemcitabine/oxaliplatin/erlotinib dose; NM- Not Measurable; NA- Not assessed; L- local recurrence; D- distant recurrence; unk- unknown