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A phase I/II trial of intensity-modulated radiation (IMRT) dose escalation with concurrent fixed- dose rate gemcitabine (FDR-G) in patients with unresectable pancreatic cancer

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Abstract

Purpose—Local failure in unresectable pancreatic cancer may contribute to death. We hypothesized that intensification of local therapy would improve local control and survival. The objectives were to determine the maximum tolerated radiation dose delivered by IMRT with FDR-G, freedom from local progression (FFLP) and overall survival (OS).

Methods and Materials—Eligibility included pathologic confirmation of adenocarcinoma, radiographically unresectable, performance status (PS) of 0–2, ANC of $\geq 1500/\text{mm}^3$, platelets $\geq 100,000/\text{mm}^3$, creatinine $< 2 \text{ mg/dl}$, bilirubin $< 3 \text{ mg/dl}$ and ALT/AST $\leq 2.5 \times \text{ULN}$. FDR-G (1000 $\text{mg/m}^2/100\text{-minutes I.V.}$) was given on days –22 and –15, 1, 8, 22, and 29. IMRT started day 1. Dose levels were escalated from 50 to 60 Gy in 25 fractions. DLT was defined as gastrointestinal toxicity Grade (G)3, neutropenic fever, or deterioration in PS to ≥ 3 between day 1 and 126. Dose level was assigned using TITE-CRM with the target DLT rate set to 0.25.

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A phase I/II trial of intensity-modulated radiation (IMRT) dose escalation with concurrent fixed-dose rate gemcitabine (FDR-G) in patients with unresectable pancreatic cancer.

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Results—Fifty patients were accrued. DLTs were observed in 11 patients: G3/4 anorexia, nausea, vomiting, and/or dehydration (7); duodenal bleed (3); duodenal perforation (1). The recommended dose is 55Gy, producing a probability of DLT of 0.24. The 2-year FFLP is 59% (95% CI: 32–79). Median and 2-year overall survival are 14.8 months (95% CI: 12.6–22.2) and 30% (95% CI 17–45). Twelve patients underwent resection (10 R0, 2 R1) and survived a median of 32 months.

Conclusions—High dose radiotherapy with concurrent FDR-G can be delivered safely. The encouraging efficacy data suggest that outcome may be improved in unresectable patients through intensification of local therapy.

Keywords

pancreatic cancer; chemoradiotherapy; IMRT; gemcitabine; local control

Introduction

Local failure is a significant clinical problem in unresectable pancreatic cancer; it is common (1) and associated with pain, gastric/duodenal obstruction, ulceration, bleeding and cholangitis. Uncontrolled local disease has also been recognized as an important cause of death (2).

Radiotherapy not only palliates symptoms, but may also impact on survival. While older trials were inconclusive, a recent ECOG phase III trial showed a survival advantage to radiation when added to gemcitabine (3). This study was closed early, but in the 71 eligible patients enrolled, median survival improved from 9.2 to 11.0 months ($p=0.044$).

Unfortunately radiotherapy in this disease has often been used suboptimally. The sensitivity of the organs in the upper abdomen has limited the radiation dose to levels that are ineffective against gross disease. Previous attempts to increase dose were unsuccessful, resulting in high morbidity and mortality (4).

Gemcitabine is a potent radiation sensitizer (5) but its use concurrently with radiation has been limited by toxicity (6–8). To maximize systemic and local control we have performed a series of trials using full-dose gemcitabine and concurrent 3D conformal radiotherapy; however, we have not been able to escalate the radiation dose beyond 36Gy (7, 9, 10). Intensity-modulated radiotherapy (IMRT) can simultaneously reduce the dose to Organs-At-Risk and allow an increase in target dose in these patients (11). Accumulation of the active phosphorylated metabolites of gemcitabine is dependent on infusion rate and can be optimized at 10 mg/m²/min (12, 13). Radiosensitization is also optimal at this rate (14). Thus, we hypothesized that intensification of local therapy, utilizing IMRT and fixed-dose rate gemcitabine (FDR-G), would result in better local control and survival. We conducted a phase I/II clinical trial to determine the maximum tolerated radiation dose delivered with IMRT and concurrent FDR-G and to estimate time to local progression and survival with this regimen.

Patients and Methods

Eligibility Criteria

The study was approved by the Institutional Review Boards. Patients had to have a pathologic diagnosis of adenocarcinoma of the pancreas, unresectable by radiographic criteria (> 180° involvement of the superior mesenteric artery or celiac trunk or unreconstructable SMV/portal vein impingement) without distant metastasis. Resectability was determined by a multidisciplinary panel of surgeons, radiologists, medical and radiation

oncologists. Borderline resectable tumors were not allowed on this study. Additional criteria included a PS of 0–2, absolute neutrophil count (ANC) of $1500/\text{mm}^3$, platelets $100,000/\text{mm}^3$, creatinine $< 2 \text{ mg/dl}$, bilirubin $< 3 \text{ mg/dl}$, ALT/AST $2.5 \times \text{ULN}$, and informed consent. Pretreatment workup included a complete history and physical examination, a complete blood count with differential, platelets, serum chemistry panel and CA 19–9 within 2 weeks of registration, and a dynamic contrast-enhanced multi-detector pancreas protocol CT (pancreatic parenchymal and portal venous phases) and chest CT within 4 weeks of registration.

Treatment regimen

Figure 1 shows a general schema of the trial. Patients received FDR-G, 1000 mg/m^2 over 100-minutes, intravenously on days 1 and 8 of a 21-day cycle. One cycle of run-in chemotherapy was given prior to IMRT. This cycle was given to help distinguish gemcitabine-related toxicity from combined modality dose-limiting toxicity by allowing pre IMRT adjustment of gemcitabine dose if needed. Patients who experienced grade (G) 4 thrombocytopenia during gemcitabine run-in treatment began protocol therapy at a 25% dose reduction. IMRT began when ANC $1,000/\text{mm}^3$, platelets $100,000/\text{mm}^3$ and all other gemcitabine related toxicity had resolved to $\leq \text{G1}$. Two cycles of FDR-G were given concurrently with IMRT (days 1, 8, 22, and 29). Post IMRT, 4 cycles of FDR-G were recommended. Dose modification of gemcitabine for hematological toxicity during a cycle was based on the ANC and platelet counts on day 8. For ANC $1,000/\text{mm}^3$ and platelets $75,000/\text{mm}^3$, full dose was given. For ANC of $500\text{--}999/\text{mm}^3$ and/or platelets of $50,000$ to $74,999/\text{mm}^3$, 50% of the dose was given. For ANC $< 500/\text{mm}^3$ or platelets $< 50,000/\text{mm}^3$, treatment (gemcitabine/IMRT) was held. Therapy was also held for $\geq \text{G3}$ non-hematological toxicity and resumed upon recovery to toxicity $< \text{G2}$. If therapy was interrupted, gemcitabine was reduced 25% when resumed.

IMRT was delivered in 25 fractions over 5 weeks. The radiation dose was escalated from 50 to 60 Gy. The Gross Tumor Volume (GTV) was defined on pancreas protocol CT. The Planning Target Volume (PTV) was GTV plus 1 cm expansion. Active Breathing Control was used to reduce/eliminate breathing motion except in 4 patients in whom 4D CT was used to generate an ITV. The six beam arrangement which was used had been previously described (11). The Organs-At-Risk constraints for IMRT planning are detailed in Table 1. Radiotherapy plans for patients enrolled outside of the University of Michigan were reviewed and approved prior to initiation of therapy.

Trial design

This phase I/II trial was designed to characterize the toxicities incurred with escalating doses of radiotherapy plus gemcitabine in patients with unresectable pancreatic cancer. The gemcitabine dose was fixed over all dose levels. The primary objective was to determine the radiation dose that is associated with dose-limiting toxicity (DLT) in 25% of patients. DLT was defined as gastrointestinal toxicity $\geq \text{G3}$, neutropenic fever, or deterioration in PS to ≥ 3 developing during IMRT or in the 13 weeks following completion of IMRT. The secondary objective was to characterize freedom from local progression (FFLP).

IMRT dose levels were assigned according to the TITE-CRM algorithm based on a simple model relating the probability of DLT (pDLT) to dose (15). This model was continually updated throughout the trial using data from all enrolled patients. Patients with partial follow-up at the time of a new enrollment were weighted by the proportion of the observation period completed. New patients were assigned to the dose estimated to have a probability closest to but not greater than the target probability of 0.25. Dose escalation was restricted to one level between sequential patients. Prior to escalation, at least one patient

must have completed the full observation period (126 days) at the previous level without DLT. Under this allocation schema, the dose increases until toxicity is observed, and then tends to vary around the dose producing the target rate.

The trial was designed to accrue fifty patients. Patients receiving at least 80% of the radiotherapy dose prescribed were considered evaluable. Patients who completed therapy but became non-evaluable before the observation period ended were counted as evaluable in the final analysis, and weighted by the proportion of the observation period for which they were evaluable. Replacements were recruited for patients who did not complete therapy for reasons unrelated to toxicity.

A simple two-parameter logistic regression model was used to estimate the pDLT at each dose level at the end of the trial. The Kaplan-Meier method was used to summarize overall survival (OS) and FFLP. The software package SAS (V9.2, Cary, North Carolina) was used for analysis.

Follow up

Patients were seen in follow up 3, 8, and 13 weeks after completion of radiotherapy and then every 2–3 months. History and physical exam, a toxicity notation, and a complete blood count, serum chemistry and CA-19–9 were obtained on each follow-up visit. CT scans of the chest abdomen (pancreas protocol) and pelvis were obtained on weeks 8, 18 and every 2–3 months thereafter. All scans were centrally reviewed by one radiologist (IRF).

Results

From 8/2006 to 5/2010, 50 patients were accrued in 2 institutions. Table 3 shows the number of assigned patients, observed DLTs, and the pDLT by dose level. The dose level closest to the target probability is 55 Gy. DLTs occurred in 11 patients and consisted of G3/4 anorexia, nausea, vomiting, and/or dehydration in 7 patients, duodenal bleed in 3 patients, and duodenal perforation in one patient. Two patients died of causes possibly related to therapy. One patient died of peritonitis assumed to be secondary to duodenal perforation; however an autopsy did not reveal a perforation. The second died of duodenal bleeding but it was not clear if this was secondary to tumor erosion into the duodenum or true toxicity. Both events were scored as DLT. Five DLTs occurred during IMRT (in the 4th and 5th week) and 6 DLTs occurred 1–12 weeks after completion of IMRT/chemotherapy.

Other severe toxicities included neutropenia (G3, 54%, G4, 2%), thrombocytopenia (G3, 13%), and anemia (G3, 11%). During the 18 week treatment/observation period 8 patients required admission; 5 secondary to DLT and 3 for reasons unrelated to protocol therapy.

All but one patient (who received 52.8 of 55 Gy prescribed) completed radiotherapy in a median time of 35 days. Eleven patients had an interruption in radiation course (4–14 days; median 8 days). In 3 of these, interruption was secondary to DLT; in 1 patient secondary to hematological toxicity; in all others it was for reasons unrelated to protocol therapy (cholangitis, lithium toxicity, sinus infection, pneumonia, other).

Gemcitabine dose reductions were required in 9 (18%) patients during run-in chemotherapy. Of these, 5 required dose reductions during IMRT as well. Eleven additional patients (22%) required reduction only during radio-chemotherapy. Dose reductions were required in 11% of administrations during the run-in period and in 13% during radio-chemotherapy.

Data on post-IMRT chemotherapy (non-protocol, but recommended, therapy) was available for 46 patients. Forty patients received FDR-G alone, one patient received gemcitabine plus

oxaliplatin and another patient received gemcitabine, capecitabine and erlotinib. The median number of cycles was 4 (range 1–6).

The median and 2-year OS are 14.8 months (95% CI 12.6–22.2) and 30% (95% CI 17–45). Only 8 patients (17%) progressed locally. The 2-year FFLP is 59% (CI 32–79). Kaplan-Meier estimates of OS and FFLP are shown in Figures 2 and 3, respectively. Twenty-nine patients (63%) progressed with distant metastasis at a median of 10.2 months. Best response was partial (33%) and stable disease (67%) and occurred at a median of 3.1 months from completion of radiotherapy. There were no complete responses.

Twelve patients underwent resection at a median of 7.5 months from start of therapy. To be considered for surgery, patients had to have significant symptomatic and radiographic improvement in degree of vascular encasement and no evidence of distant metastases. Complete clearance of all soft-tissue around the celiac artery or SMA was not required, as our prior experience suggested that such residual could represent treatment-related fibrosis. Surgical procedures included Whipple resection in 10 patients and distal pancreatectomy in 2 patients. Of these, 6 patients required venous or arterial repair/reconstruction. Pathologic responses were CR: 2 patients, near-CR: 3 patients and PR: 7 patients. Resection margins were negative in 10 patients and microscopically positive in 2. Median length of stay following surgery was 7 days (range 5–12). Thirty day post-operative all-cause mortality was 8%, with a single sudden death of unclear cause. Patients who underwent resection had a median OS of 32 months and FFLP of 92%.

Discussion

In this trial we have established that high-dose radiotherapy (55Gy in 25 fractions) can be administered safely with concurrent full-dose FDR-G, with IMRT delivered during breath hold. The rate of severe toxicity (24%) observed at this dose is similar to the 26% rate of severe G3/4 non-hematological toxicities reported in a recent phase 2 trial (16) using our previous gemcitabine-based radio-chemotherapy regimen. Thus, for an equivalent toxicity, we were able to escalate the biological effective dose by approximately 60%. We also found encouraging signals of efficacy when compared to our historical controls (median and 2-year survival of 14.8 months and 30%, respectively, versus 11.2 months and 13% previously) (1).

The therapeutic ratio is also improved when compared to other contemporary trials in this patient population. For instance, on a recent RTOG phase II trial (17) patients received bevacizumab concurrent with capecitabine and radiation (50.4 Gy in 28 fractions) followed by bevacizumab and gemcitabine. G 3 GI toxicity was 35.4% (22% during radio-chemotherapy) and median survival was 11.9 months. Chauffert et al (18) reported on 119 patients randomized to intensive induction radio-chemotherapy (60 Gy in 30 fractions with concomitant 5-FU and cisplatin) or induction gemcitabine. Maintenance gemcitabine was given in both arms. G 3 toxicity during induction therapy developed in 36% and 22% of the treatment arms, respectively. Additional toxicity was observed during maintenance therapy (32% and 18% for the two arms, respectively). Median OS was 8.6 and 13 months, respectively.

A secondary objective of our trial was to determine the impact of high-dose radiotherapy on FFLP. We found that escalation of the radiation dose improved the 2-year FFLP from 38% in our historical controls (1) to 59%. Others (19) have also documented poor local control, 20% at 2 years, with external-beam radiotherapy (40–60 Gy) with or without concurrent 5-FU. Given the low radiation dose traditionally used in this disease, these poor rates of local control come as no surprise. Although the relationship between local control and radiation

dose is not well documented, a recent analysis of unresectable patients treated with intraoperative and external-beam radiotherapy found a significant improvement with doses above 50Gy (20). At lower doses, the rate of local control beyond 2 years was only about 25%. Unfortunately, delivery of radiation doses adequate to control gross disease has been severely limited by the sensitivity of the organs in the upper abdomen and previous attempts to increase dose were unsuccessful, resulting in significant morbidity and mortality (4).

Failure to control the primary tumor results not only in significant morbidity but may possibly increase mortality. We have previously observed that local failure is an independent predictor of OS, even when distant metastatic spread is accounted for in a multivariate analysis (1). More direct evidence comes from an autopsy series documenting that 30% of patients with pancreatic cancer died of complications of locally destructive disease (2). Finally, a recent ECOG phase III trial showed a 2-months survival advantage to the combination of radiotherapy and gemcitabine over gemcitabine alone (3), presumably mediated by an improvement in local control. Our results, showing an apparent improvement in both local control and survival, lend further support to the notion that survival may be improved in patients with unresectable pancreatic cancer through intensification of local therapy.

Another novel finding in this trial is that 12 of 50 patients (24%) initially judged unresectable by an experienced multi-disciplinary panel were able to undergo resection with good outcomes; 10 patients (83%) had R0 resection and 5 patients (42%) had a major pathological response. The median survival in these patients was 32 months. Importantly, we found that residual abnormalities next to blood vessels can often represent fibrotic tissue with no malignant cells. The results demonstrate that major pancreatic surgery can be performed safely (by an experienced pancreatic surgeon) after high-intensity therapy; however, the contribution of resection to survival is not clear. It is possible that the favorable survival in this group is a reflection of their response to radio-chemotherapy and selection of those who had not progressed.

The strengths of this trial include a modern and efficient TITE-CRM design that allowed us to determine the tolerable radiation dose and the efficacy of this regimen simultaneously. All clinical decisions were made by a multi-disciplinary tumor board, a process that reduced selection bias. Patients with borderline-resectable disease were not included since we had a different concurrent trial for these patients. A potential weakness is the fact that the trial was conducted in highly specialized centers. It is unknown how these results might apply to patients treated in a community setting. Also, we have not utilized FDG-PET in determining eligibility. Thus, the patients treated on this trial may have included some with occult metastatic disease that may have been detected by PET. The use of PET might have led to better outcomes through stage migration, but also could have contributed to better selection of patients for an intensive course of radiation and chemotherapy.

In summary, we show that intensity-modulation and breath-hold techniques allowed escalation of the radiation dose with concurrent FDR-G and resulted in encouraging outcomes. These results also suggest that survival may be improved in patients with unresectable pancreatic cancer through intensification of local therapy, a hypothesis that needs to be tested in a larger multi-institutional trial. This regimen has become part of our new standard in patients with borderline or unresectable disease which now includes a more prolonged and intensified systemic induction phase.

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Summary

Local failure in pancreatic cancer may contribute to death. We conducted a phase I/II trial in 50 patients with unresectable pancreatic cancer to determine the maximum tolerated dose delivered by IMRT with FDR-G, freedom from local progression (FFLP) and overall survival (OS). We found that 55 Gy in 25 fractions was well tolerated. The 2-year FFLP and OS were encouraging, 59% and 30%, respectively. Twelve patients underwent resection (10 R0) and survived a median of 32 months.

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	Run-in period			Study period					Observation Period
	Wk -3	Wk -2	Wk -1	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 8-18
IMRT				X	X	X	X	X	
Gemcitabine	X	X		X	X		X	X	X

IMRT Dose escalation: 45Gy (1.8Gy/fraction) to 60 (2.4Gy/fraction)

Gemcitabine 1000 mg/m², 100-minute infusion, d -22, d -15, d1, d8, d22, d29

Post IMRT, beginning any time after week 7, up to 4 cycles of single agent gemcitabine may be administered using the same schedule (day 1, 8 every 21 days)

Figure 1. Trial schema

A general schema of the trial. The trial started with one 3-week cycle of run-in FDR-G. This was followed by 5 weeks of concurrent FDR-G and dose-escalated IMRT. After completion of IMRT patients were observed for additional 13 weeks for the development of DLT. During this observation period, additional chemotherapy was allowed (single agent gemcitabine was recommended).

Figure 2. Overall survival

Kaplan Meier plot of overall survival. The median and 2-year overall survival are 14.8 months (95% CI: 12.6–22.2) and 30% (95% CI 17–45).

Figure 3. Freedom from local progression

Kaplan Meier plot of Freedom from Local Progression. The 2-year FFLP is 59% (95% CI: 32–79).

Table 1

Constraints for IMRT planning

Structure	Constraints
Kidney (Left & Right)	Maximum dose 20Gy; not more than 10% of the volume can be between 18 and 20Gy
Liver	Mean dose 30 Gy; Minimize mean dose
Stomach/ Small intestine	Maximum dose 54Gy; 2% of the volume can be between 50 and 54Gy, 25% of the volume can be between 45 and 54Gy
Spinal cord	Maximum dose 45Gy
Duodenum	Maximum dose prescribed dose; not more than 33% of the volume can be between 45 and prescribed dose

Table 2

Patient and tumor characteristics

Characteristic	Value
Age (years)	
Median	63
Range	48–83
Sex	
Male	30 (60%)
Female	20 (40%)
Race	
Caucasian	40 (80%)
African American	6 (12%)
Other	4 (8%)
Tumor location	
Head	33 (66%)
Neck	10 (20%)
Body/Tail	7 (14%)
Tumor size (cm)	
Median/Mean	3.25/3.7
Range)	1.6–7.1
Tumor volume (cc)	
Median/Mean	47.9/69.1
Range	17–170
Baseline CA-19-9 (U/mL)	
Median/Mean	102/837
Range	11–5028

Table 3

Number of patients assigned to each dose level and the probability of DLT

Level	Dose (Gy)	No. patients treated	No. DLTs	Posterior p(DLT)	Estimated* p(DLT)
1	45	0	0	0.13	.04
2	50	5	0	0.16	.08
3	52.5	17	2	0.19	.14
4	55	20	6	0.23	.24
5	57.5	8	3	0.26	.39
6	60	1	0	0.27	.55

* From maximum likelihood fit of 2 parameter logistic regression model.