

CLINICAL INVESTIGATION

Gastrointestinal Cancer

PHASE I STUDY OF CONFORMAL RADIOTHERAPY AND CONCURRENT FULL-DOSE GEMCITABINE WITH ERLOTINIB FOR UNRESECTED PANCREATIC CANCER

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Purpose: To determine the recommended dose of radiotherapy when combined with full-dose gemcitabine and erlotinib for unresected pancreas cancer.

Methods and Materials: Patients with unresected pancreatic cancer (Zubrod performance status 0–2) were eligible for the present study. Gemcitabine was given weekly for 7 weeks (1,000 mg/m²) with erlotinib daily for 8 weeks (100 mg). A final toxicity assessment was performed in Week 9. Radiotherapy (starting at 30 Gy in 2-Gy fractions, 5 d/wk) was given to the gross tumor plus a 1-cm margin starting with the first dose of gemcitabine. A standard 3 plus 3 dose escalation (an additional 4 Gy within 2 days for each dose level) was used, except for the starting dose level, which was scheduled to contain 6 patients. In general, Grade 3 or greater gastrointestinal toxicity was considered a dose-limiting toxicity, except for Grade 3 anorexia or Grade 3 fatigue alone.

Results: A total of 20 patients were treated (10 men and 10 women). Nausea, vomiting, and infection were significantly associated with the radiation dose ($p = .01$, $p = .03$, and $p = .03$, respectively). Of the 20 patients, 5 did not complete treatment and were not evaluable for dose-escalation purposes (3 who developed progressive disease during treatment and 2 who electively discontinued it). Dose-limiting toxicity occurred in none of 6 patients at 30 Gy, 2 of 6 at 34 Gy, and 1 of 3 patients at 38 Gy.

Conclusion: The results of the present study have indicated that the recommended Phase II dose is 30 Gy in 15 fractions. © 2012 Elsevier Inc.

Pancreas cancer, Phase I, Conformal radiotherapy, Gemcitabine, Erlotinib.

INTRODUCTION

Gemcitabine has been the primary chemotherapy drug for locally unresectable pancreas cancer (1) for a number of years. This recommendation was determined from a randomized trial, predominantly involving patients with metastatic disease, that found a modest improvement in median survival of 5.7 months after with gemcitabine treatment compared with 4.4 months with 5-fluorouracil (5-FU) alone and an improved palliative response (2). Later studies also supported gemcitabine use, including a randomized trial of resected disease that found that adjuvant gemcitabine therapy for 6 months was superior to observation (3). Also, a trial of locally unresectable disease found that early administra-

tion of gemcitabine alone was superior to delaying gemcitabine by about 2 months to deliver chemoradiotherapy with cisplatin and 5-FU (4).

The addition of the oral, targeted agent, erlotinib to gemcitabine provided a significant benefit in a randomized trial (5), again that had predominantly included patients with metastatic disease. The benefit of the addition of erlotinib was small, with a median survival of 6.3 months vs. 6 months but a 1-year survival rate of 23% vs. 17% for gemcitabine with erlotinib compared with gemcitabine alone, respectively (5). Adding erlotinib increased the toxicity, with any Grade 3 or 4 toxicity developing in 62% of patients in the erlotinib arm compared with 57% in the gemcitabine-alone arm. Despite some reservations regarding the degree of

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benefit and the minimally increased toxicity of this combination, the significance of the findings led to approval by the Food and Drug Administration and the recommendation that therapy with this combination should be considered for patients with locally advanced, unresectable disease (6).

A previous Phase I study determined that full-dose gemcitabine could be safely combined with short-course radiotherapy (RT) to the gross disease without inclusion of clinically negative lymph node-bearing areas (7). Preclinical studies using pancreatic cancer cells have found that gemcitabine is a marked radiation sensitizer, even at noncytotoxic concentrations (8) and that the addition of erlotinib to gemcitabine plus RT enhanced tumor growth delay (9), suggesting that the combination of all three agents, gemcitabine, erlotinib, and RT, could result in improved control of both local and distant sites. The present Phase I study was performed to determine the safe dose of radiation when concurrently administered with full-dose gemcitabine and erlotinib.

METHODS AND MATERIALS

Eligibility

Patients with pancreatic cancer were considered eligible for the present trial if they had had histologic confirmation of pancreatic adenocarcinoma, unresected disease, a life expectancy of ≥ 12 weeks, a Zubrod performance status of 0–2, an absolute granulocyte count of $\geq 1,500/\text{mm}^3$, platelet count of $\geq 100,000/\text{mm}^3$, blood urea nitrogen of not $>30 \text{ mg}\%$, creatinine $<1.5 \text{ mg}\%$, and no previous abdominal RT or any chemotherapy within the previous 4 weeks. Patients with metastatic disease were eligible because the previous study of full-dose gemcitabine with conformal RT had allowed selected patients with metastatic disease and found survival was equivalent to those without metastatic disease. Measurable disease was not required because the response was not monitored. The human investigation committee of William Beaumont Hospital approved the present study. All patients provided written informed consent before therapy.

The pretreatment evaluation required a complete history and physical examination, baseline assessments of organ function, chest X-ray or chest computed tomography (CT), and abdominal CT within the previous 2 months.

Treatment

The patients were seen at least once a week during protocol therapy, with a final toxicity assessment in Week 9. Thus, all participants were observed for ≥ 1 month after completion of the RT portion of the regimen to ensure observance of subacute toxicity. After the final toxicity assessment, the subjects were off the study and underwent additional therapy at the discretion of the patient and their attending medical oncologist. The participants were removed from the study for disease progression during treatment, a treatment interruption of >2 weeks, failure to complete RT, life-threatening toxicity, or patient refusal. If participants were removed from treatment, they were not considered in the analysis of the dose escalation unless a dose-limiting toxicity (DLT) had occurred before treatment removal.

Gemcitabine was given as a 30-minute intravenous infusion at a dose of $1,000 \text{ mg}/\text{m}^2$ once a week for 7 weeks, preferably on each Monday of the week. Dose adjustments of gemcitabine were made according to the parameters published in the Food and

Drug Administration-approved package insert. A complete blood count was obtained before each dose of gemcitabine, including the absolute granulocyte count (AGC) and platelet count. A full dose of gemcitabine was given if the AGC was $\geq 1,000 \text{ mm}^3$ and the platelet count was $\geq 100,000 \text{ mm}^3$. A 25% dose reduction was given for an AGC of ≥ 500 but $<1,000 \text{ mm}^3$ and/or a platelet count of $\geq 50,000$ but $<100,000 \text{ mm}^3$. The dose was held for an AGC of $<500 \text{ mm}^3$ or a platelet count of $<50,000 \text{ mm}^3$. If the hematologic toxicity recovered to a platelet count of $>100,000 \text{ mm}^3$ (Grade 0) and/or Grade 0–2 AGC within 1 week after a treatment hold, gemcitabine was resumed at a 25% dose reduction for the next dose only and at full dose for the subsequent weeks unless toxicity recurred. Colony-stimulating factors were allowed for hematologic toxicity at the discretion of the attending medical oncologist. If hematologic toxicity did not recover within 2 weeks, the protocol therapy was discontinued.

Erlotinib was given once daily by mouth at a dose of 100 mg, 7 d/wk for 8 weeks. The management of rash and diarrhea was as recommended for gefitinib (10). If Grade 3 or 4 diarrhea occurred and was unresponsive to antidiarrheal medications, the dose of erlotinib was reduced first to 75 mg/d and then to 50 mg/d or discontinued. The occurrence of Grade 3 or 4 total bilirubin, aspartate aminotransferase, or alanine aminotransferase elevation during treatment could result in a dose reduction or interruption of erlotinib. This was left to the discretion of the treating physicians and was dependent on the presence of recently treated biliary obstruction or concurrent RT, because both of these situations can independently result in elevated liver function test findings.

All subjects underwent a treatment planning CT scan in the treatment position with a custom immobilization cradle and both oral and intravenous contrast. The gross tumor volume was outlined to contain the primary tumor and any visibly enlarged regional lymph nodes. The clinical target volume was the gross tumor volume plus 0.5 cm, except where this would include a clearly uninvaded structure, typically the vertebral bodies or stomach. The planning target volume (PTV) was the clinical target volume plus 0.5 cm. RT was given using a standardized three-field technique with an anterior to posterior and two lateral fields designed to encompass the PTV within the 95% isodose line and giving 100% to the isocenter. Planning also kept any point along the spinal cord to $\leq 44 \text{ Gy}$, $\geq 75\%$ of the combined kidney volume to a dose of $\leq 20 \text{ Gy}$, and the mean liver dose to $\leq 30 \text{ Gy}$. If 75% of the combined kidney volume could not be kept to $\leq 20 \text{ Gy}$, one kidney was allowed to be irradiated to a dose $>20 \text{ Gy}$, as long as the other kidney received a maximum of 12 Gy and was functional on intravenous contrast studies or renal perfusion scanning.

Radiotherapy was started after the first dose of gemcitabine on Day 1 and was given for 5 d/wk at a dose of 2 Gy/d, with the number of treatment sessions and total dose determined by the dose-escalation schedule. If gemcitabine was withheld during a week in which RT was scheduled, the RT was also withheld and was resumed when the gemcitabine was resumed.

Dose escalation

The starting dose of RT was 30 Gy in 15 fractions, with each subsequent dose level achieved by adding an additional two fractions and extending treatment into the fourth and fifth weeks. The highest possible dose level was planned to be 50 Gy within 25 fractions.

Dose escalation was accomplished in standard Phase I fashion with 3-person cohorts, except for the starting dose, which was to contain 6 patients. If none of the 3 patients had developed a DLT, escalation occurred to the next highest dose level (except for the

starting dose level). If 1 of 3 patients had developed a DLT, an additional 3 patients were enrolled to that dose level. If 1 of the 6 patients at a dose level developed a DLT, escalation continued to the next higher dose level. If 2 of 3, or 2 of 6 patients at any dose level, developed a DLT, the maximal tolerable dose was exceeded and escalation was stopped. Accrual was then continued at the next lower dose level until ≥ 6 patients were treated at that dose level. If the final dose level had 0 or 1 DLT, it was declared the recommended dose for Phase II evaluation.

Definition of DLT

Toxicity was defined using the National Cancer Institute/Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events, version 3.0 (11). DLT was defined as Grade 3 or greater thrombocytopenia that failed to resolve to Grade 0 within 1 week. Grade 4 or greater neutropenia that failed to resolve to Grade 2 or less within 1 week was also considered DLT. Grade 3 nausea or vomiting, gastrointestinal hemorrhage that was Grade 2 (1 to 2 U of blood transfused) or greater, Grade 4 anorexia or fatigue unaccompanied by another DLT, and any Grade 3 or greater toxicity in other organ system (except hyperbilirubinemia due to biliary obstruction, aspartate aminotransferase/alanine aminotransferase elevations considered due to RT or after biliary obstruction, or any grade of alopecia) were also considered DLTs.

Statistical analysis

A Pearson chi-square test was used to analyze the relationship between the radiation dose and the development of toxicity. An analysis of variance estimated model was used to test the relationship of the PTV and the development of nausea, vomiting, diarrhea, or fatigue.

RESULTS

Patient characteristics

A total of 20 patients (10 men and 10 women; median age, 63 years; age range, 47–86) were treated. Of the 20 patients, 2, had Stage IB, 4 had Stage IIA, 2 had Stage IIB, 8 had Stage III, and 4 had Stage IV disease. At presentation, 12 patients

had moderate to severe pain. Also, 5 patients had had endobiliary stents placed before therapy.

Toxicity

The overall acute and subacute toxicity was acceptable (Table 1). A statistically significant relationship was found between Grade 0 and Grade 1 or greater nausea ($p = .01$), vomiting ($p = .03$), and infection ($p = .03$). Grade 3 nausea and vomiting typically occurred in Weeks 6 and 7, well after RT had been completed. One patient in the 30-Gy group developed Grade 3 thrombocytopenia that had resolved to Grade 0 within 1 week and was not considered a DLT. No renal toxicity developed.

Of the 20 patients, 3 were removed during the trial because of progressive disease (at 34, 38, and 38 Gy), and 2 chose to discontinue therapy (at 22 and 30 Gy). None of these 5 patients had exhibited a DLT; however, because they had not completed the planned RT and chemotherapy regimen, they were not included for dose-escalation purposes, and another patient was accrued to the same dose level in their place. None of the 6 patients treated to 30 Gy experienced a DLT, and none of the initial 3 patients, although 2 of 3 additional patients treated to 34 Gy experienced a DLT (Grade 3 nausea and vomiting), and 1 of 3 patients treated to 38 Gy had developed a DLT (Grade 4 fatigue). One patient at the 34-Gy level had developed Grade 3 neutropenia with Grade 3 cellulitis during Week 8, which was not considered a DLT.

The median PTV was 272 cm³ (range, 95–684), which was significantly related to fatigue ($p = .03$), but was unrelated to nausea, vomiting, or diarrhea ($p > .05$).

DISCUSSION

The role of RT combined with 5-FU was established by randomized trials performed by the Gastrointestinal Tumor Study Group (12, 13). With the development of

Table 1. Toxicity

Toxicity	Dose 30 Gy			Dose 34 Gy			Dose 38 Gy		
	Grade 0	Grade 1-2	Grade 3-4	Grade 0	Grade 1-2	Grade 3-4	Grade 0	Grade 1-2	Grade 3-4
AGC	4	3	0	0	6	1	2	4	0
Platelet count	2	4	1	0	5	2	1	4	1
AST	2	4	1	1	6	0	3	3	0
ALT	0	5	2	1	5	1	1	5	0
Bilirubin	5	2	0	6	1	0	2	3	1
Nausea	4	3	0	0	5	2	0	6	0
Vomiting	6	1	0	2	3	2	1	5	0
Diarrhea	4	3	0	3	3	1	2	4	0
Anorexia	4	3	0	2	4	1	0	3	3
Dyspnea	7	0	0	7	0	0	5	1	0
Thrombosis	7	0	0	7	0	0	5	1	0
Rash	3	4	0	4	3	0	3	3	0
Infection	6	1	0	6	0	1	1	1	4
Pain	1	2	4	1	3	3	0	3	3
Fatigue	2	5	0	2	3	2	0	5	1

Abbreviations: AGC = absolute granulocyte count; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

gemcitabine-based chemotherapy; however, the role of RT became uncertain. The initial Phase I studies of an escalating gemcitabine dose combined with RT using traditional treatment fields and/or traditional radiation doses found severe upper gastrointestinal toxicity with a gemcitabine dose >250 mg/m² to 440 mg/m² weekly (14–16), leading some investigators to question whether the therapeutic ratio of chemoradiotherapy still favored 5-FU-based treatment (17). A number of clinical trials have been performed using lower doses of gemcitabine once (14–16) or twice weekly (18), decreasing the dose and/or volume of RT (19), or avoiding concurrent administration of gemcitabine and RT altogether (20). Ultimately, the determination of the role of RT will require a randomized trial, rather than simply eliminating the RT portion because of toxicity concerns.

Although each of the approaches to combined modality therapy can be criticized for some form of theoretical compromise, reasons exist to continue to study this combination. Gemcitabine is a strong radiosensitizer. Preclinical studies have found that radiation enhancement ratios of about 1.7 occurred even with noncytotoxic concentrations of gemcitabine (8). Also, solid preclinical (9) and clinical (21) evidence has shown that the addition of an epidermal growth factor receptor inhibitor, such as erlotinib, enhances the radiation effect.

Therefore, the combination of gemcitabine, erlotinib, and RT offers the possibility of improved local control from the combination treatment and improved distant control because of the chemotherapy. The local control rates have not been well reported, probably because it has been easier to assess distant failure with CT scans. Also, when close attention was paid to local control, the median interval to local progression was only 6.4 months with full-dose gemcitabine and short-course RT (19). Although it can be argued that local progression would be irrelevant in a disease with a high risk of systemic relapse, it could also be argued that overall tumor control will not occur without long-term local control and that the bulk of the local disease is the likely source of treatment resistant clonogens.

Recent evidence has shown that the combination of gemcitabine and RT might be superior to gemcitabine alone. Although currently presented in abstract form only, an Eastern Cooperative Oncology Group randomized trial that was closed early because of poor accrual reported an improved median survival of 11 months with gemcitabine and RT compared with 9.2 months with gemcitabine alone ($p = .04$) (22). Results such as this will need to be repeated; however, the outcome from the only randomized trial of gemcitabine vs. gemcitabine with RT supports continued study.

The minimal dose intensity of gemcitabine necessary for a systemic benefit is unknown. The randomized trials that established the value of gemcitabine for locally advanced or metastatic disease (2) and resected disease (3) both administered 1,000 mg/m² as a 30-min infusion once each week. The strongest evidence suggesting that gemcitabine dose intensity matters was found in the randomized trial of 60 Gy of RT, cisplatin, and 5-FU followed by gemcitabine

vs. gemcitabine alone (4). In that trial, the chemoradiotherapy arm did markedly worse, leading to early closure of the study. On analysis of treatment delivery, the subjects receiving chemoradiotherapy had had more toxicity and had received significantly less gemcitabine than had the subjects in the gemcitabine-only arm, although the survival difference could also have been related to the minimal 10-week delay in gemcitabine administration in the chemoradiotherapy arm. Differences in gemcitabine dose intensity were also found between responders and nonresponders with pancreatic cancer (23) and in retrospective studies of lung cancer that found an improved response and survival associated with a relative dose intensity of $\geq 80\%$ (24).

Thus, the studies that lowered the dose of gemcitabine to be able to deliver concurrent RT (14–16, 18) might have had the same problem as the chemoradiotherapy vs. gemcitabine trial (4) when tested in a randomized fashion against gemcitabine alone, namely that the lower dose of gemcitabine led to reduced systemic control and early failure. Maintaining the gemcitabine at a full dose and reducing the radiation dose and/or volume is probably the optimal strategy for a randomized trial.

Ample evidence has now shown that RT can be safely given concurrently with full-dose gemcitabine. Five studies have reported on a short course of RT, typically 36 Gy within 15 fractions, to a reduced radiation field, with encouraging Phase I and II results but no randomized trials (7, 19, 25–27). Six studies of a more standard course of RT, typically 45–50 Gy within 5 weeks have been reported (28–32), including the use of intensity-modulated RT (33). The shared characteristic among all these studies was an effort to reduce the size of the irradiated volume, usually by treating only the grossly involved areas. Larger studies with more toxicity events and efforts to escalate the dose using intensity-modulated RT techniques would be helpful to further define the normal tissue tolerances using this approach. Ultimately, as more experience accumulates, it might be possible to safely individualize the radiation dose according to the PTV and normal tissue volumes irradiated.

The present study was the only study that has combined RT with full-dose gemcitabine and erlotinib. Two other studies have used all three agents; however, one trial gave only 75 mg/m² gemcitabine with paclitaxel weekly (34) and one gave 40 mg/m² gemcitabine twice weekly during RT (35). Both were dose-escalation trials of erlotinib and would have been difficult to compare for toxicity with the present experience, because of the differences in chemotherapy dose and schedule.

In contrast to the previous Phase I trial of full-dose gemcitabine with RT that found 36 Gy within 15 fractions was the recommended dose (7), the present trial found that 30 Gy within 15 fractions was the recommended Phase II dose. Because the predominant toxicity was gastrointestinal, this difference in the tolerable dose supported enhanced radiation sensitization of the gastrointestinal tract with the concurrent administration of erlotinib. However, the toxicity could also have simply been related to extending RT into the

fourth week of gemcitabine, which was not done in the previous trial (7).

Although 30 Gy within 15 fractions was a lower total radiation dose than in the studies combining RT with 5-FU (12, 13), the effective dose would be expected to be much greater because of radiation sensitization. If each radiation dose of 2 Gy was sensitized by a factor of 1.7, such as was found for noncytotoxic conditions (8), the equivalent amount was 3.4 Gy/d to 51 Gy, a substantial radiation dose within a short period.

CONCLUSION

On the basis of the results of the present trial, we have begun a Phase II study of the combination of full-dose gemcitabine and erlotinib, with 30 Gy radiation in 15 fractions, as was determined from the present trial. Because of the timing of the nausea, vomiting, and fatigue observed, the RT will be given in Weeks 5–7, instead of Weeks 1–3, allowing Week 8 to be an erlotinib-only week. We anticipate that this minor modification will further enhance the tolerance of this combination.

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