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ORIGINAL ARTICLE

Two phase I studies of concurrent radiation therapy with continuous-infusion 5-fluorouracil plus epirubicin, and either cisplatin or irinotecan for locally advanced upper gastrointestinal adenocarcinomas

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Abstract
Purpose Multimodality therapy with chemotherapy and radiation treatment may improve disease control and overall outcome of locally advanced upper gastrointestinal (UGI) malignancies including esophageal, gastric, pancreatic, and biliary tract carcinomas. However, more effective and less toxic chemotherapy regimens with concomitant radiotherapy are needed beyond concurrent continuous-infusion fluorouracil (CIFU) with radiation that is commonly applied in general practice. Epirubicin, cisplatin, and irinotecan are active cytotoxic chemotherapy agents in UGI cancers.
Methods Two parallel phase I studies were designed to test the tolerability (dose-limited toxicity [DLT] and maximum tolerable dose [MTD]) of the combination of radiotherapy concurrently with CIFU, epirubicin, and cisplatin (ECF/radiation) or CIFU, epirubicin, and irinotecan (EIF/radiation) in the treatment of locally advanced upper GI malignancies. CIFU was administered through a portable infusion pump for 5 1/2 weeks during radiation treatment (50.4 Gy–a dose of 45 Gy in 25 fractions of 1.8 Gy, with additional comedown of 5.4 Gy). Epirubicin, cisplatin, or irinotecan were administered intravenously each week for 5 weeks (days 1, 8, 15, 22, and 29).
Results The MTDs recommended for further studies are: 5-fluorouracil 200 mg/m^2/day CI, weekly cisplatin 20 mg/m^2 and epirubicin 10 mg/m^2 for ECF/radiation combination; 5-fluorouracil 200 mg/m^2/day CI, weekly irinotecan 30 mg/m^2 and epirubicin 10 mg/m^2 for EIF/radiation regimen. The DLTs are neutropenia, diarrhea/dehydration, and mucositis as expected.
Conclusions Both regimens are safe with expected toxicities, and the efficacy of both regimens was encouraging. Further larger scale studies should be considered.

Keywords Concurrent chemoradiation · Upper GI malignancies · Epirubicin, cisplatin, irinotecan, 5-FU (fluorouracil) · Dose-limited toxicity (DLT) · Maximum tolerable dose (MTD)

Introduction

Upper gastrointestinal (UGI) cancers are common and highly virulent diseases that include esophageal, gastric, pancreatic, and biliary tract cancers. Based on the American Cancer Society's estimates, there will be 16,470 esophageal, 21,130 gastric, 42,470 pancreatic, and nearly 20,000 biliary cancers diagnosed in 2008 in the United States [1]. The overall prognoses of these diseases are disappointing. Although recently developed chemotherapy regimens have shown some improvement in the treatment of advanced UGI adenocarcinomas, most have only modest clinical efficacy. Even for patients with resected disease, the rate of recurrence—including local failure and distant metastasis—is very high. Improvement in survival will rely on the development of effective multimodality treatment plans.

Combinations of chemotherapy and radiotherapy have demonstrated survival benefits in patients with locally advanced unresectable adenocarcinomas of the esophagus, gastroesophageal junction, stomach, and pancreas [2–4].

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Survival advantages have also been shown with perioperative chemoradiation in GI cancers [5–7]. Infusional fluorouracil (CIFU) has been commonly given concurrently with radiation for locally advanced upper GI adenocarcinomas.

Epirubicin is a semisynthetic derivative of doxorubicin. The antitumor activity of epirubicin, like that of other anthracyclines, results from intercalation between DNA base pairs and stabilization of the topoisomerase II DNA complexes, leading to irreversible DNA strand breakage [8]. It has been estimated that epirubicin is about 25% less myelotoxic and 50% less cardiotoxic than doxorubicin. Cisplatin is a heavy metal compound, which has the activity of a bifunctional alkylating agent, and has a broad spectrum of antitumor activity. Combinations of 5-FU and cisplatin have been considered as the reference regimen for advanced gastric cancer. The ECF regimen of (epirubicin, cisplatin, CIFU) resulted in a significant response and survival benefit for advanced unresectable and metastatic esophagogastric cancer [9–12]. Long-term follow-up of a prospectively randomized study demonstrated an advantage with the ECF compared to FAMTX [13]. The overall response rate was 46% with ECF with the median survival 8.7 and the 2-year survival of 14%.

Results of a recently reported phase III study showed that pre- and postoperative ECF increases the rate of complete resection of locally advanced gastric cancer [14]. This study also demonstrated improved disease-free survival and overall survival in patients who had ECF treatment before and after surgery, compared to those who had surgery alone. Results from several phase II studies suggest that ECF may prolong survival in patients with locally advanced or metastatic pancreatic cancer with tolerable toxicities [15–17].

Irinotecan, a camptothecin derivative, is a topoisomerase I inhibitor that traps the topoisomerase I/DNA cleavable complex following cleavage of single-strand DNA. Collision of the replication fork converts the single-strand break into a double-strand break, thus inducing apoptosis. The antitumor activity of irinotecan has been well documented in colorectal cancer [18]. In upper GI malignancies, irinotecan has shown significant activity as a single agent [19] and also in combination with 5-FU and cisplatin [20, 21]. In vitro and animal studies with epirubicin and camptothecins have demonstrated synergistic antitumor activity with enhanced DNA damage and tumor cell killing [22].

A randomized study compared concurrent chemoradiation with epirubicin (60 mg/m^2) with external-beam radiotherapy (40 Gy in fractions of 2.5 Gy four times a week for 4 consecutive weeks) to radiation alone in 220 patients with locally advanced cervical cancer [23]. The result demonstrated a survival benefit in the chemoradiation arm, with increased mild- to moderate marrow suppression (no grade 4 leukopenia or grade 3 thrombocytopenia). There was no difference in treatment delays observed between the two arms, and no increased skin or normal organ toxicity.

Based on these data, we sought to evaluate the feasibility and tolerability of radiotherapy with ECF (epirubicin, cisplatin, and CIFU) or EIF (epirubicin, irinotecan, and CIFU) chemotherapy concurrently for locally advanced upper GI adenocarcinomas.

Patients and methods

Patients were eligible for these two studies if they had histologically confirmed adenocarcinoma of the esophagus, stomach (including gastroesophageal junction), pancreas, and biliary tract, with locally advanced unresectable disease or in whom postsurgery pathology showed positive margins or with gross regional residual disease. Patients with adenocarcinoma of the esophagus, pancreas, and biliary tract status postresection and who were considered to have a high risk of recurrence (T3, T4, and/or lymph node metastases) were also acceptable, if they would have been treated with CIFU and radiation off-protocol. Patients must have been older than 18 years with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, and adequate organ function defined as white blood cell count $\geq$ 3,000/mm^3, absolute neutrophil count $\geq$1,500/mm^3, platelet count $\geq$100,000/mm^3, serum creatinine $\leq$2.0 mg/dl, total bilirubin $\leq$2.0 mg/dl, and AST/ALT $\leq$2.5 $\times$ ULN, and a left ventricular ejection fraction of at least 50%. Patients who had previous chemotherapy or radiation treatment were excluded from the trials. Pregnant or lactating women were also excluded. Written informed consent was obtained from all patients. This study was approved by the institutional review board of the Hospital of the University of Pennsylvania.

Study design

Two parallel open-label nonrandomized, dose-escalating phase I studies were designed to test the feasibility and define dose-limiting toxicity (DLT) and maximum tolerable doses (MTD) of the combination of concurrent radiation therapy with CIFU, epirubicin, and cisplatin (ECF) or CIFU, irinotecan, and epirubicin (EIF) in patients with locally advanced upper gastrointestinal adenocarcinoma. A secondary objective was to preliminarily assess efficacy of these two combinations in those patients with measurable or evaluable diseases. The studies were open in parallel as planned breaks for evaluation of dose levels allowed for continued enrollment in the alternative study by standard '3 + 3' design.

5-Fluorouracil was administered as a continuous intravenous infusion via an implantable port through a portable

infusion pump for 28 days during radiation treatment and was started at the day one of radiation. Epirubicin, cisplatin, or irinotecan were each administered as a 60- to 90-min infusion weekly for 5 weeks. Administration of epirubicin, cisplatin, or irinotecan was started on day 1 of radiation (days 1, 8, 15, 22, and 29 of the treatment plan) (Fig. 1).

All patients underwent a CT simulation with 3D treatment-planning. Patients were treated with radiation beams ≥6 MV, and a minimum of 3 treatment fields were used. All fields were treated each day with five fractions delivered weekly. The treatment volume was determined by the site of origin of the tumor with inclusion of regional lymph nodes in the target volume. All patients were treated with customized blocks or multileaf collimator. The volume was treated to a dose of 45 Gy in 25 fractions of 1.8 Gy, with an additional comedown of 5.4 Gy to a total dose of 50.4 Gy. Dose was prescribed to the isocenter of the treatment plan, and the maximum dose variation within the target volume was within 5% of isocenter dose. Treatment was continuous except when interrupted for hematologic or gastrointestinal toxicity.

Growth factors and prophylactic antibiotics were not given routinely while patients were on study. For nutritional support, most patients had feeding tubes (either G- or J-tubes) placed and tube feeding was administered based on need upon the recommendation of an oncologic nutritionist. All patients were seen by medical oncologists weekly with laboratory work including CBC, kidney, and liver function tests during their chemoradiation courses.

The dose-escalation schedules of the studies are listed in Tables 1 and 2. Dose-limiting toxicities (DLT) attributed to studies were defined as toxicities related to the treatment requiring discontinuation or significant dose reduction in study drugs, which include at least one of the followings: (1) absolute neutrophil count (ANC) less than 500/mm^3 lasting greater than 5 days; (2) ANC less than 1,000/mm^3 with fever

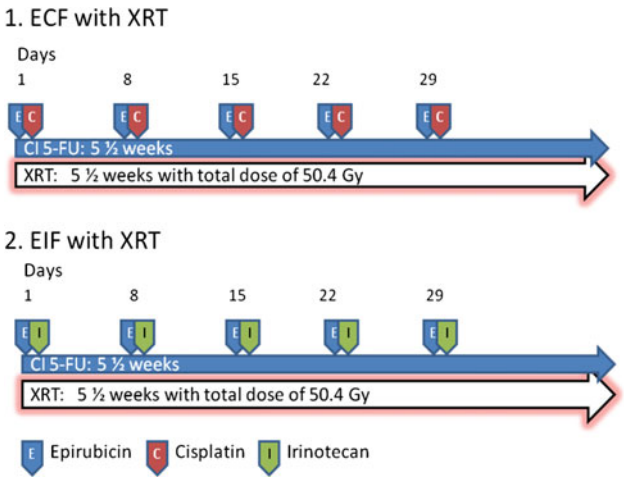

Fig. 1 Schema of the studies

Table 1 Doses and escalations in the ECF/XRT study

Level	5-FU (24 h) (mg/m^2/day)	Cisplatin (mg/m^2)	Epirubicin (mg/m^2)
1	200	20	10
2	225	20	10
3	225	20	15
4	250	20	15
5	250	25	15
6	250	25	20
7	250	25	25

ECF epirubicin/cisplatin/5-FU, *5-FU* fluorouracil

Table 2 Doses and escalations in the EIF/XRT study

Level	5-FU (24 h) (mg/m^2/day)	Irinotecan (mg/m^2)	Epirubicin (mg/m^2)
1	200	30	10
2	225	30	10
3	225	30	15
4	225	30	20
5	225	40	20
6	250	40	20
7	250	50	20
8	250	50	25

EIF epirubicin/irinotecan/5-FU, *5-FU* fluorouracil

greater than 38.5°C; (3) platelet count less than 25,000/mm^3; (4) grade 3 diarrhea despite maximal loperamide support; (5) receipt of less than 75% of the planned dose of all three drugs in a cycle; (6) nonhematologic toxicity ≥CTC grade 3. Toxicities were assessed according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) scale. The maximum tolerated dose (MTD) was defined as one dose level below the dose that induced dose-limiting toxicity in greater than one-third of patients in a given cohort. The dose modification was designed based on the type (hematologic vs. nonhematologic) and grade of toxicities.

Results

Fourteen patients were enrolled in the ECF/radiation study and all were evaluable for toxicity and response; 11 patients enrolled in the EIF/radiation study (Tables 3, 4) with 10 patients evaluable for toxicity and response.

DLT and recommended dose

In the ECF/radiation study, there was no DLT observed at dose level 1 in the initial 3 patients. At dose level 2, one of

Table 3 Characteristics of patients in the ECF/XRT study

Number entered/evaluable	14/14
Males/females	12/2
Median age (range)	56.5 year (41–70 year)
Performance status	
0	10
1	4
Primary tumor site	
Pancreatic	8
Duodenal	1
Gastric/GEJ	1/4

Table 4 Characteristics of patients in the EIF/XRT study

Number entered/evaluable	11/10
Males/females	8/3
Median age (range)	61 year (42–79 year)
Performance status	
0	3
1	8
Primary tumor site	
Pancreatic	5
Cholangio/bile duct	5
Gastric (gastroesophageal junction)	1

the first three patients developed grade 4 neutropenia; four more patients were added to this level, and one of 4 additional patients had a DLT with grade 3 dehydration and was admitted to the hospital. Based on the data from the level 2, additional 4 patients were enrolled back to dose level 1. With seven patients enrolled at this dose level, none experienced a DLT. Therefore, dose level 1 (5-fluorouracil 200 mg/m^2/day continuously infusion during radiation, cisplatin 20 mg/m^2, weekly for 5 weeks, and epirubicin 10 mg/m^2, weekly for 5 weeks) was the MTD recommended for further study.

In the study of EIF/radiation, a 79-year-old patient with locally advanced biliary cancer at level 1 developed severe diarrhea (grade 3) and dehydration (grade 4) after her third dose of chemotherapy requiring monitoring in the medical intensive care unit. She recovered from the event and was taken off study. Because of this event, however, an extra 4 patients were added to the level 1 (6 patients in total), and no additional DLT occurred. At level 2, 2 out of 5 patients developed DLTs (grade 3 dehydration and grade 3 mucositis). Therefore, dose level 1 (5-fluorouracil 200 mg/m^2/day continuously infusion during radiation, irinotecan 30 mg/m^2, weekly for 5 weeks, and epirubicin 10 mg/m^2, weekly for 5 weeks) was the MTD and also the recommended dose for further studies.

Table 5 Hematologic toxicity of ECF/XRT

Level	*N*	Neutropenia					Thrombocytopenia				
		0	1	2	3	4	0	1	2	3	4
1	7	5	1	1	–	–	2	5	–	–	–
2	7	2	3	–	1	1[a]	2	4	1	–	–

[a] DLTs: 1 case with Gr.4 Neutropenia, 1 case with Gr. 3 Dehydration and hospitalized

Table 6 Hematologic toxicity of EIF/XRT

Level	*N*	Neutropenia					Thrombocytopenia				
		0	1	2	3	4	0	1	2	3	4
1	6*	2	2	2	1*	–	4	2	1*	–	–
2	5	2	3	–	1	1	2	4	1	–	–

* A 79-year-old patient did not follow medical advice, developed severe dehydration after 3 treatments, and was admitted to ICU

Overall toxicity

All patients were assessable for toxicity. Hematologic toxicities were observed in both levels of the ECF/radiation and EIF/radiation studies. Overall, there were 5 patients who developed grade 1/2 neutropenia, 1 patient had grade 3 neutropenia, and 10 patients had grade 1/2 thrombocytopenia in the ECF/radiation study (Table 5). Similarly, there were 7 cases of grade 1/2 neutropenia and 4 cases of grade 1/2 thrombocytopenia observed in the EIF/radiation study (Table 6).

Fatigue, nausea, vomiting, diarrhea, dehydration, and mucositis were the main nonhematologic toxicities (Tables 7, 8). There was grade 2 nausea/vomiting at all levels of the study. There were three cases of Port-a-Catheter-related upper extremity DVT (deep vein thrombosis) in the EIF trial (two in the level 1 and one in the level 2), other grade 1/2 toxicities included hyperglycemia, hypokalemia, hypomagnesemia and all of them were corrected.

Efficacy

Although assessment of tumor response was not a primary objective of this study, treatment efficacy was assessed in patients with measurable diseases. The concurrent administration of either ECF or EIF with radiation effected disease control (SD + PR + CR) rate of 75% (9/14 in the ECF/XRT study and 9/10 in the EIF/XRT study).

In the ECF/radiation study, with a total of 14 evaluable patients, 9 patients achieved at least stable disease (7 SD, 1 PR, and 1 CR). Three locally advanced GEJ patients with cancer were enrolled with one case initially considered to be unresectable (T3N2) after CT/MRI/EUS (endoscopic ultrasound) analysis. All patients successfully underwent

Table 7 Nonhematologic toxicity of ECF/XRT

Level	*N*	Nausea/vomiting				Diarrhea				Dehydration				Mucositis				Fatigue			
		0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3
1	7	1	1	5	–	6	–	1	–	6	–	1	–	7	–	–	–	5	2	–	–
2	7	1	1	5	–	3	2	1	1	4	–	–	3[a]	4	1	1	1	2	1	3	1

[a] DLTs: 1 case with Gr.4 Neutropenia, 1 case with Gr. 3 Dehydration and hospitalized

Table 8 Nonhematologic toxicity of EIF/XRT

Level	N	Nausea/vomiting				Diarrhea				Dehydration					Mucositis				Fatigue				DVT			
		0	1	2	3	0	1	2	3	0	1	2	3	4	0	1	2	3	0	1	2	3	0	1	2	3
1	6*	3	1	1	1*	3	2	–	1*	4	–	1	–	1*	5	–	–	1*	4	–	1	1*	3 (4*)	–	–	2[a]
2	5	1	1	3	–	2	1	1	1	2	–	1	2[b]	–	2	–	1	2[b]	1	–	4	–	4	–	–	1[a]

* A 79-year-old patient did not follow medical advice, developed severe dehydration after 3 treatments, and was admitted to ICU

She was removed from the study

[a] Port-A-Cath-related blood clot

[b] DLTs: 2 cases Gr. 3 dehydration and Gr. 3 mucositis

surgery. One patient achieved pathological complete response; one had partial response with his disease down-staged (N1 pre-chemoradiation to pathological N0). Among 8 patients with locally advanced pancreatic cancer, 4 patients had stable disease, with CA19-9 decreased in 3 cases and normalized in one patient. One patient with T4N1 duodenal adenocarcinoma which was initially considered unresectable had a Whipple procedure after ECF/XRT, and pathology results showed an ypT3N0 tumor. Three more cycles of chemotherapy were given postoperatively. The patient has remained free of disease for more than 18 months.

In the EIF study, 10 patients were evaluable for response. Eight patients had SD (3 cholangiocarcinoma, 4 pancreatic cancer, and 1 gastroesophageal junction adenocarcinoma) and one achieved PR (gallbladder cancer). The patient with gastroesophageal junction adenocarcinoma thought to be initially unresectable had complete surgical resection for his disease. The patient who had locally advanced unresectable gallbladder cancer received additional chemotherapy following the completion of combined modality therapy and is alive more than 5 years after treatment.

Discussion

The role of chemotherapy and radiation combination as either pre-operative therapy or for definitive treatment in locally advanced UGI malignances has been generally accepted; however, a standard chemotherapy regimen has yet to be defined, and debate exists regarding the role of radiation therapy when surgery is performed [2–5, 24–27]. The combination of different chemotherapy agents may increase the effectiveness of therapy for both locally advanced and metastatic disease [28, 29]. However, with the concerns regarding toxicity and safety, concurrent chemoradiation therapy has been limited with 5-FU as the only chemotherapy agent. Some of the debate about the efficacy of the combined modality therapy in the resectable population likely relates to the limitations of the chemotherapy and potential less systemic coverage [27, 30]. Therefore, it is needed to develop better chemoradiation therapy combinations for controlling upper GI cancers more effectively, both locally and systemically. The data from these two phase one studies are encouraging and demonstrate a tolerable toxicity profiles for either ECF/radiation or EIF/radiation. There were no unexpected toxicities and no treatment-related mortality. Based on the recommended dose of either combinations, the dose of continual infusion of 5-FU is close to the dose when 5-FU is given concurrently with radiation as a single agent. The cumulative doses of chemotherapy agents in 5 weeks are epirubicin 50 mg/m^2, cisplatin 100 mg/m^2, and irinotecan 150 mg/m^2, which are more than the half doses while they are given without therapeutic radiation and may have significant effects in disease control systemically. Larger studies of either regimen with concurrent radiation are warranted even when we are moving into target-oriented therapy era.

One important message from these two studies is that supportive care, especially nutritional support, is very important to maintain patients on treatment. All patients worked directly with a nutritionist that specialized in gastrointestinal malignancies treated in the multimodality set-

ting. All of our patients had feeding tubes, and majority of them used their feeding tubes for nutrition of rehydration during the treatment courses.

The MTDs of both of these regimens have been established. The ECF/XRT regimen is of particular interest, since the gastric cancer trial of perioperative ECF demonstrated both disease-free and overall survival advantages compared to surgery alone [14]. A large randomized trial (CALGB 80101) has just finished patient enrollment, comparing standard 5-FU before, during, and after radiation to an experimental regimen of ECF before and after radiation, but with only CIFU during radiation. If the experimental arm of this trial demonstrates benefit, the data for the feasibility and dose of ECF given with radiation concurrently from our trial may be utilized to increase drug exposure for adjuvant regimens and for locally advanced gastric and gastroesophageal tumors.

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