A Phase II Study with Cetuximab and Radiation Therapy for Patients with Surgically Resectable Esophageal and GE Junction Carcinomas

Hoosier Oncology Group G05-92

Carlos R. Becerra, MD, Nasser Hanna, MD,† Andrew David McCollum, MD,* Naftali Becharm, MD,‡ Robert D. Timmerman, MD,§ Michael DiMaio, MD,§ Kenneth A. Kesler, MD,‖ Menggang Yu, PhD,‖ Tong Yan, PhD, MS,‖ and Hak Choy, MD§*

Introduction: On the basis of the promising activity of cetuximab and radiation therapy for head and neck cancers, we evaluated the efficacy of this regimen followed by surgery in patients with resectable esophageal cancer. This was a phase II, open-label, single-arm, multicenter study of patients with potentially resectable esophageal cancer.

Methods: Patients received two weekly doses of cetuximab followed by weekly cetuximab combined with radiation therapy for 6 weeks. After a 6- to 8-week rest, patients' primary tumor was resected. The main objective was to evaluate pathologic complete response (pCR) rate in the primary tumor after cetuximab and radiation therapy.

Results: Thirty-nine patients completed the study. Most patients were men (93%), median age was 64 years, performance status was 0 to 1 (95%), patients had a histology of adenocarcinoma (78%), and tumors were located in the esophagus (63%). Grade 3 toxicities in more than 5% of patients included dysphagia (17%), anorexia and dehydration (7%), and dyspnea, fatigue, hypernatremia (5%). Grade 5 aspiration occurred in 2% (1 patient). Four patients died, two from disease progression, one from aspiration pneumonia postsurgery, and one from septic shock. Thirty-one patients (76%) underwent esophagectomy. The pCR rate was 36.6% by intention-to-treat and 48% for patients who underwent esophagectomy. The pCR by histology was 6 of 9 (67%) for squamous cell carcinomas and 9 of 32 (28%) for adenocarcinoma. Earlier-stage disease was associated with increased pCR (IIA 70%, IIB 29%, III 28%).

Conclusions: Cetuximab and radiation therapy results in a pCR rate that seems at least comparable with that of chemotherapy and radiation therapy. This regimen may be better tolerated than preoperative chemotherapy and radiation therapy in patients with resectable esophageal cancers.

(*J Thorac Oncol.* 2013;8: 1425–1429)

Key Words: Esophageal, Cetuximab, Radiation therapy, Resectable.

Esophageal carcinomas in 2012 affected 17,460 Americans, resulting in an estimated 15,070 deaths.[1] One standard approach for the management of patients with resectable esophageal cancer involves trimodality therapy that includes chemotherapy with concurrent radiation therapy followed by surgical resection of the primary lesion with improved long-term survival but marginal tolerance to treatment.[2,3] Patients who cannot have surgical resection of the esophagus cancer can be treated with combined chemotherapy and radiation therapy with superior survival outcomes similar to those with radiation alone.[4]

The epidermal growth factor receptor (EGFR) signaling pathway is an important target in esophageal cancers, and high EGFR expression by immunohistochemical score in the tumor of patients with resected esophageal adenocarcinomas after trimodality therapy predicts a poor outcome.[5] Cetuximab is a monoclonal antibody that binds to the EGFR and competitively inhibits the binding of epidermal growth factor and other ligands blocking phosphorylation and activation of receptor-associated kinases. EGFR inhibition results in Gap 1 cell-cycle arrest, and radiation results in Gap 2 cell-cycle arrest, Gap 1 and Gap 2 being part of the interphase segment of cell growth. In preclinical models, EGFR inhibition enhances radiation-induced apoptosis, inhibits repair of radiation-induced DNA damage, and inhibits formation of new blood vessels.[6] The radio-sensitizing effect of cetuximab has already been tested in patients with squamous cell

*US Oncology Research, McKesson Specialty Health, The Woodlands, Texas, and Texas Oncology-Baylor Sammons Cancer Center, Dallas, Texas; †Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, Indiana; ‡Community Oncology Center, Kokomo, Indiana; §University of Texas Southwestern Medical Center at Dallas, Dallas, Texas; and ‖Indiana University School of Medicine, Indianapolis, Indiana.

Disclosure: Carlos R. Becerra is on the speakers' bureau for Eli Lilly and company. A.D. McCollum is a consultant for Genentech. Hak Choy is Chairman of Radiation Oncology at UT Southwestern Medical Center and is a consultant for Bristol-Meyers-Squibb and Eli Lilly. All the other authors declare no conflict of interest.Abstract part of this study (Abstract No. 4557) was published at the 2009 American Society of Clinical Oncology Annual Meeting (*J Clin Oncol* 2009;8:1425–1429).

Address for correspondence: Carlos R. Becerra, MD, Texas Oncology, Baylor Sammons Cancer Center, 3410 Worth Street, Dallas Texas 75246. E-mail: carlos.becerra@usoncology.com

ISSN: 1556-0864/13/0811-1425

carcinomas of the head and neck, with improvement in local control, progression-free and overall survival over radiation therapy alone.[7]

Herein, we present the results of a single-arm, open-label, phase II study with cetuximab and external beam radiation therapy for patients with newly diagnosed, potentially resectable esophageal and gastroesophageal (GE) junction carcinomas, with the intent of improving efficacy and decreasing toxicity over current standard treatment approaches.

MATERIALS AND METHODS

This was a phase II, open-label, single-arm, multicenter study that accrued patients with potentially resectable esophageal cancer. The study was conducted in accordance with the Declaration of Helsinki and is consistent with International Conference on Harmonisation good clinical practice guidelines. The protocol was approved by the local institutional review boards/ethics committees, and all patients provided a written informed consent. The study was coordinated by the Hoosier Oncology Group Clinical Trials Working Group (Indianapolis, IN).

The primary objective of the study was to evaluate the pathologic complete response (pCR) rate in the primary tumor after cetuximab and radiation therapy. Secondary objectives were to evaluate the clinical complete and partial response rates, and overall toxicities.

Patients

Key inclusion criteria were the following: age more than 18 years; Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2; pathologic diagnosis of squamous cell carcinoma or adenocarcinoma of the esophagus or GE junction; clinical stages IIA, IIB, III, or IVA with celiac node involvement; surgical candidates as determined by a surgical consult; patient being agreeable to surgical resection of the primary tumor; no prior use of radiation or chemotherapy for cancer of the esophagus or GE junction; no prior therapy directed against the EGFR pathway; no major surgeries within 28 days of registration for protocol therapy; no other active malignancies; no history of uncontrolled cardiac disease; no history of interstitial pneumonitis or pulmonary fibrosis; and adequate marrow and organ function including absolute neutrophil count more than 1000 mm^3; platelet count more than 75,000 mm^3, hemoglobin more than 10 g/dl, creatinine less than two times the upper limit of normal (ULN), bilirubin less than 2.5 times ULN, aspartate transaminase (SGOT), and/or alanine aminotransferase (SGPT) less than 5.0 times ULN; no prior severe infusion reaction to a monoclonal antibody; and use of an effective method of contraception.

Treatment

All patients received premedication with dyphenhydramine hydrochloride at an initial dose of 50 mg by intravenous infusion given 30 to 60 minutes before the first dose of cetuximab. Premedication with dyphenhydramine hydrochloride for subsequent doses of cetuximab was modified at the investigators' discretion.

The initial dose of cetuximab was administered at 400 mg/m^2 intravenously over 120 minutes followed by weekly infusions of cetuximab at 250 mg/m^2 over 60 minutes. Cetuximab was administered weekly for two doses. Radiation therapy was started after the second dose of cetuximab, and the combination of once-weekly cetuximab and radiation therapy was continued until the completion of radiation therapy. Total weekly cetuximab doses equaled eight.

External beam radiation therapy was started on week 3 of cetuximab infusion to a total dose of 50.4 Gy divided into 1.8 Gy per fraction per day. Megavoltage equipment was required with effective photon energies at more than 6 MV. Twice weekly, the verification films of orthogonal views were reviewed by the treating physicians.

All study patients had a planned surgical resection of the primary tumor and adjacent mediastinal and/or celiac lymph nodes after satisfactory hematologic and functional recovery within 8 weeks of completion of radiation therapy. Lymph node staging performed at the time of laparoscopy or thoracoscopy was repeated at the time of resection. Rather than simply sampling a site-representative node from each level, we removed all technically accessible lymph nodes.

Assessment

Efficacy

Patients had a baseline computed tomography scan of the chest, abdomen, and pelvis with repeat imaging performed after cetuximab and radiation therapy to exclude interim development of metastatic disease. Patients had a baseline upper endoscopy with ultrasound, pulmonary function tests, and tumor sampling. Clinical staging was reported according to the American Joint Commission on Cancer criteria version 6.[8] At the time of surgery, an evaluation of the primary sample was performed to determine complete pathologic response (defined as the absence of tumor cells in the resected specimen).

Safety and Tolerability

A safety evaluation was performed at baseline and then weekly for the duration of treatment. Patients were followed for 12 weeks after surgical resection or until resolution of treatment-related toxicities. Patients underwent a physical examination, vital signs, ECOG performance status, complete blood count, and chemistries as part of the safety evaluation. Toxicities were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0,[9] and this included assessment of dysphagia as follows:

Grade 0: None
Grade 1: Mild dysphagia but can eat a regular diet
Grade 2: Dysphagia requiring predominantly liquids, pureed foods, or soft diet
Grade 3: Dysphagia requiring a feeding tube, intravenous hydration, or parenteral hyperalimentation
Grade 4: Complete obstruction (cannot swallow saliva); ulceration with bleeding not induced by minor trauma or abrasion or perforation.

Adverse events not covered by the National Cancer Institute Common Terminology Criteria for Adverse Events criteria were graded according to a three-point system: mild, moderate, and severe.

Statistical Methods

The efficacy of the treatment was evaluated using Simon's two-stage minimax design where the endpoint variable was pCR. The null hypothesis was that the probability of pCR was 0.20. The alternative hypothesis was that the pCR was 0.35. A type I error of 0.10 and a type II error of 0.20 were selected. A total of 22 patients were enrolled in the first stage, and at least five pCRs were required to enroll an additional 19 patients in the second stage. If the number of pCRs exceeded 11, then the alternative hypothesis would be accepted.

During the first stage of the efficacy analysis, the impact of any nonhematologic toxicities exceeding grade 2 would be assessed with two sets of stopping rules, one for grade 4 toxicities and another for grade 3 or grade 4 toxicities. If the boundaries of grade 3 or 4 toxicities were reached (i.e., 5 of 22 patients) in the first phase of the trial, the study would be terminated.

RESULTS

The characteristics of the patients enrolled in the study are delineated in Table 1. The majority of the patients were men (93%), median age was 64 years, and they had an ECOG performance status of 0 to 1 (95%); patients had a histology of adenocarcinoma (78%), and tumors were located in the esophagus (63%).

Drug Exposure

Cetuximab was given at day −14 (loading dose), day −7, chemoradiation therapy week 1 to week 6, all together 8 weeks. Thirty-seven patients (90%) received 8 weeks of cetuximab. Radiation therapy was given during chemoradiation therapy week 1 to week 6, all together 6 weeks. Thirty-nine patients (95%) received 6 weeks of radiation therapy. Patients who completed treatment per protocol were either those who completed 8 weeks of cetuximab and 6 weeks of radiation therapy or those who missed part of the per protocol treatment but underwent the surgery. Thirty-nine patients (95%) completed the study treatment (Table 2).

Dose Modification and Dose Delay

Please refer to Table 3. Cetuximab required dose modification because of toxicity (17%), planned per protocol (5%), or because of intercurrent illness (2%). Cetuximab was delayed because of toxicity (10%), intercurrent illness (2%), or scheduling (5%). The dose of radiation therapy was modified because of toxicity (7%) or scheduling (24%).

TABLE 1. Patient Characteristics

Characteristics	Category/Statistics	*n*/Value	%
Sex	Female	3	7
	Male	38	93
Race	White	36	88
	Black or African American	4	10
	Unknown	1	2
Ethnicity	Hispanic or Latino	2	5
	Non-Hispanic	37	90
	Not reported	2	5
Age	Median	64	
	Minimum	50	
	Maximum	82	
	Mean	64.5	
	SD	6.9	
PS	0	26	63
	1	13	32
	2	2	5
Tumor site	Esophagus	26	63
	Gastroesophageal junction	15	37
Disease stage	IIA	10	24
	IIB	7	17
	III	22	54
	IVA	2	5
Histology	Squamous cell carcinoma	9	22
	Adenocarcinoma	32	78

ITT population ($n = 41$).
PS, performance status; ITT, intent-to-treat.

TABLE 2. Study Treatment Compliance

	Cetuximab	Radiation Therapy
Patients Treated	**N = 41 (%)**	**N = 41 (%)**
Number of weeks receiving treatment		
0		1 (2)
1	1 (2)	1 (2)
3	1 (2)	
4	1 (2)	
7	1 (2)	
6		39 (95)
8	37(90)	
Statistical summary of weeks protocol treatment received		
Median	8	6
Minimum	1	0
Maximum	8	6
Mean	7.6	5.7
SD	1.4	1.2
Total number of patients who completed protocol treatment	39 (95)	

TABLE 3. Dose Delay

Drug	Dose Delay	*n*	%
Cetuximab	Toxicity	4	10
	Intercurrent illness	1	2
	Scheduling (patient or site)	2	5

ITT population ($n = 41$).
ITT, intent-to-treat.

TABLE 4. Grade 3 Toxicities ≥5% Irrespective of Causality Attributed

	Grade 3	
CTCAE	**N**	**%**
Anorexia	3	7
Dehydration	3	7
Dysphagia	7	17
Dyspnea	2	5
Fatigue	2	5
Hypernatremia	2	5

ITT population ($n = 41$). Grade 4 and 5 toxicities did not occur in ≥5% of patients.
CTCAE, Common Terminology Criteria for Adverse Events; ITT, intent-to-treat.

Patients came off study if protocol-defined follow-up was completed (56%), if there was symptomatic deterioration (10%), or if they were lost to follow-up (7%), had died because of disease progression (5%) or other causes (5%), or for other reasons, that is, disease progression after restaging evaluation and before surgery (17%).

Toxicity

Table 4 shows grade 3 toxicities seen in more than 5% of patients. No grade 4 toxicities occurred in more than 5% of patients, and one grade 5 toxicity occurred in 2% of patients. Each occurrence of toxicity is the highest level each patient reported, irrespective of causality attributed. The most frequent toxicity for all grades was dysphagia (88%) followed by acneiform rash (76%), nausea (46%), and fatigue (39%). The most frequent grade 3 toxicities occurring in more than 5% of patients were dysphagia (17%), dehydration (7%), and anorexia (7%). Grade 5 toxicities included aspiration and infection, each reported in one patient (2%).

Four patients died during the study, two because of disease progression, one because of aspiration pneumonia after surgery, and one because of septic shock.

Pathological Response

Thirty-one patients (76%) underwent esophagectomy. Of these, 15 (48%) had a pathologic complete response (pCR; 95% confidence interval [CI], 30%–67%), and 16 (52%) had no pCR ; 95% CI, 33%–70%). The pCR percentage rate was higher in earlier-stage disease and in patients with squamous histology (Table 5). There was no significant difference in pCR for tumors of the esophagus (35%) versus GE junction (40%).

TABLE 5. Pathologic Complete Remission by Initial Clinical Stage and Histology

Stage or Histology	pCR	%
IIA	7/10	70
IIB	2/7	29
III	6/22	27
IVA	0/2	0
Adenocarcinoma	9/32	28
Squamous cell	6/9	67

pCR, pathologic complete response.

Ten patients (24%) patients did not have surgery. Seven had metastatic disease on restaging evaluation before surgery and were taken off study. One patient was taken off study because of treatment-related complications, one patient developed bilateral lower extremity critical lower limb ischemia, and one declined surgery after a restaging positron emission tomography scan revealed no evidence of active disease. Thirty-six patients (88%) reported dysphagia while on the study. Twenty-six patients (63%) reported dysphagia relief.

DISCUSSION

In this phase II study, the addition of cetuximab to external beam radiation therapy in patients with potentially resectable esophageal cancers resulted in a pCR rate of 36.6% by intention-to-treat analysis and 48% in patients who had esophagectomy. Patients with earlier-stage of disease and squamous histology had a higher percentage of pCR. The combination regimen was well tolerated; the most frequent toxicities included rash, nausea, and fatigue, with more than 90% of patients completing the scheduled treatment before surgery.

pCR as a surrogate marker of improved clinical outcome has been reported in several studies and has been the subject of a recent meta-analysis.[10] Scheer et al.[10] reported a meta-analysis on the effect of pCR on overall survival. The patients with tumors that went into a pCR had a median overall survival of 37.4 months versus 19.6 months ($p = 0.011$) for patients with persistent disease after combined chemotherapy and radiation therapy. Thus, the pCR rate seems to be a valid clinical surrogate endpoint for studies with chemotherapy and radiation therapy in esophageal cancers.

The role of neoadjuvant chemotherapy and radiation therapy in patients with potentially resectable esophageal adenocarcinomas and squamous cell carcinomas has been the subject of large phase III randomized studies with mixed results. Walsh et al.[2] randomized 113 patients with resectable esophageal adenocarcinoma to surgery or cisplatin/5FU and radiation therapy to 40 Gy followed by surgery. The pCR rate was 25%. Surgical mortality was reported as 12% and 4% in the experimental and control arm, respectively with estimated survival of 32% versus 6% at 3 years. In the Cancer and Leukemia Group B 9781 study,[3] 475 eligible patients were planned to be randomized to esophagectomy with lymph node dissection or trimodality therapy followed by esophagectomy. The study was closed prematurely because of poor accrual after 56 patients were enrolled (30 in the trimodality therapy arm and 26 in the surgery-only arm). The pCR rate in the trimodality arm of the study was 40% in patients with available data and 33.3% by intention-to-treat analysis. Two patients (7.7%) in the trimodality arm did not have surgery, because of evidence of metastatic disease. The median survival (4.48 versus 1.79 years) and 5-year survival (39% versus 16%) favored the trimodality arm of the study over surgery alone.[3] Despite the early termination of the study, small sample size, and overlapping CIs, the study provides additional evidence of the benefit of neoadjuvant trimodality therapy for patients with potentially resectable esophageal cancer.

Safran et al.[11] reported on a phase II clinical trial of cetuximab in combination with weekly paclitaxel, carboplatin, and radiation therapy for patients with esophageal adenocarcinomas. The complete clinical response rate was 70%. Grade 3 and 4 toxicity included cetuximab-related rash (23%) and esophagitis (15%). In a phase Ib/II study,[12] 28 patients with resectable esophageal adenocarcinoma and squamous cell carcinomas received two 3-week cycles of cisplatin, docetaxel, and cetuximab followed by radiation therapy, weekly cisplatin, and cetuximab. No limiting toxicity occurred, and the three main toxicities included esophagitis, anorexia, and fatigue. Surgery was performed in 25 patients. Anastomotic leak occurred in three patients. The rate of complete pathologic response was 32%, and the event-free and estimated survival at 12 months was 82% and 86%, respectively.

Leichman et al.[13] reported on a phase II clinical trial with oxaliplatin, 5-fluorouracil and external beam radiation therapy on 93 patients with resectable esophageal and GE junction adenocarcinomas. Seventy-three patients (78.5%) had esophagectomy, the R0 resection rate was 67.7%, and the pCR rate was 28%. The death rate resulting from chemoradiation therapy or surgery complications while on study was 4.4%. In a study by Spigel et al.[14] on neoadjuvant docetaxel, oxaliplatin, capecitabine, and radiation therapy, 31% of the patients never made it to surgery because of declining performance status, patient request, death, physician decision, and disease progression. In our study, 24% (10 of 41) of patients with resectable disease did not undergo surgery, 17% (7 of 41) because of development of metastatic disease on restaging evaluation. Although multiagent chemotherapy seems to control micrometastatic disease, the toxicities of the regimen result in poor patient tolerance and an increased rate of complications.

Although we can only speculate among studies, our study compares favorably, the drug regimen was very well tolerated, and it had a very high rate of pCRs, raising the question of the need for concomitant chemotherapy, radiation therapy, and an EGFR-blocking agent. Sequencing of the agents might be more appropriate to incorporate chemotherapy into the schedule and possibly reduce the rate of systemic recurrence.

Our study has limitations. We did not collect information on tumor location and did not perform a complete assessment of dysphagia, which may be helpful information in the management of esophageal cancer.

ACKNOWLEDGMENTS

This study was supported by a grant from Bristol-Meyers Squibb.

REFERENCES

1. Cancer Facts & Figures 2012. Atlanta, GA: American Cancer Society, 2012: No. 500812.
2. Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TP. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. *N Engl J Med* 1996;335:462–467.
3. Tepper J, Krasna MJ, Niedzwiecki D, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. *J Clin Oncol* 2008;26:1086–1092.
4. Herskovic A, Martz K, al-Sarraf M, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Engl J Med* 1992;326:1593–1598.
5. Gibson MK, Abraham SC, Wu TT, et al. Epidermal growth factor receptor, p53 mutation, and pathological response predict survival in patients with locally advanced esophageal cancer treated with preoperative chemoradiotherapy. *Clin Cancer Res* 2003;9:6461–6468.
6. Pueyo G, Mesia R, Figueras A, et al. Cetuximab may inhibit tumor growth and angiogenesis induced by ionizing radiation: a preclinical rationale for maintenance treatment after radiotherapy. *Oncologist* 2010;15:976–986.
7. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med* 2006;354:567–578.
8. AJCC Cancer Staging Handbook, 6th Ed. New York, NY: Springer-Verlag, 2002.
9. National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 (CTCAE). Washington, DC: National Cancer Institute, 2006. Available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf. Accessed March 9, 2011.
10. Scheer RV, Fakiris AJ, Johnstone PA. Quantifying the benefit of a pathologic complete response after neoadjuvant chemoradiotherapy in the treatment of esophageal cancer. *Int J Radiat Oncol Biol Phys* 2011;80:996–1001.
11. Safran H, Suntharalingam M, Dipetrillo T, et al. Cetuximab with concurrent chemoradiation for esophagogastric cancer: assessment of toxicity. *Int J Radiat Oncol Biol Phys* 2008;70:391–395.
12. Ruhstaller T, Pless M, Dietrich D, et al. Cetuximab in combination with chemoradiotherapy before surgery in patients with resectable, locally advanced esophageal carcinoma: a prospective, multicenter phase IB/II Trial (SAKK 75/06). *J Clin Oncol* 2011;29:626–631.
13. Leichman LP, Goldman BH, Bohanes PO, et al. S0356: a phase II clinical and prospective molecular trial with oxaliplatin, fluorouracil, and external-beam radiation therapy before surgery for patients with esophageal adenocarcinoma. *J Clin Oncol* 2011;29:4555–4560.
14. Spigel DR, Greco FA, Meluch AA, et al. Phase I/II trial of preoperative oxaliplatin, docetaxel, and capecitabine with concurrent radiation therapy in localized carcinoma of the esophagus or gastroesophageal junction. *J Clin Oncol* 2010;28:2213–2219.

