A Phase II Trial of Preoperative Concurrent Chemotherapy/Radiation Therapy Plus Bevacizumab/Erlotinib in the Treatment of Localized Esophageal Cancer

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Abstract: *Purpose*: To evaluate the efficacy of bevacizumab (Avastin, Genentech) and erlotinib (Tarceva, Genentech/Roche) when added to preoperative chemoradiation therapy with paclitaxel, carboplatin, and infusional 5-fluorouracil (5-FU) in the treatment of localized cancers of the esophagus or gastroesophageal (GE) junction. The primary endpoint was the pathologic complete response (pCR) rate. *Methods*: Eligible patients had previously untreated localized squamous cell, adenocarcinoma, or adenosquamous carcinoma of the esophagus or GE junction, and were considered surgical candidates at enrollment. Daily erlotinib (100 mg orally) was administered on days 1–42 of preoperative treatment. Patients received paclitaxel (200 mg/m^2 intravenously [IV]), carboplatin (area under the curve [AUC] 5.0 IV), and bevacizumab (15 mg/kg IV) on days 1 and 22, and 5-FU by continuous infusion (225 mg/m^2/day IV) on days 1–35, with radiation therapy in 1.8-Gy single fractions, Monday–Friday (to a total of 45 Gy). Those who were deemed surgical candidates proceeded to resection during weeks 12–14. *Results*: Between February 2007 and September 2009, 62 patients (median age, 64 years; 92% male; 94% adenocarcinoma) were enrolled; 44 patients (71%) completed neoadjuvant treatment and proceeded to surgery. Eighteen patients (29%) achieved pCR, with partial pathologic remission in an additional 22 patients (35%). Common grade 3/4 toxicities included leukopenia (64%), neutropenia (44%), mucositis/stomatitis (42%), diarrhea (27%), and esophagitis (27%). There were 40 instances of treatment-related hospitalization, and 2 postoperative deaths. *Conclusions*: The addition of bevacizumab and erlotinib to neoadjuvant chemoradiation did not demonstrate survival benefit or improved pCR rate over similar regimens. While the overall rates of toxicity were not increased, targeted agent–specific toxicity was evident. Further study of this specific regimen is not warranted.

Background and Rationale

Esophageal cancers and cancers of the gastroesophageal (GE) junction are increasing in incidence in the United States. In 2011, there were 16,980 new diagnoses of esophageal cancer and 14,710 deaths, yielding an 87% fatality rate.[1] This increased incidence rate is due to an increase in adenocarcinomas, likely secondary to multiple factors, including obesity. In contrast, squamous cell carcinomas have a decreasing incidence rate.[2] Most patients who are successfully treated for esophageal cancer have early-stage disease and are able to undergo definitive surgical resection. The addition of neoadjuvant chemoradiation has improved treatment results when compared to surgical resection alone,[3] and is currently the most commonly used treatment approach in the United States. However, the 5-year survival of 20% with this approach remains inadequate. It has been shown that the pathologic complete response rate (pCR) after neoadjuvant treatment correlates with overall clinical outcome for patients with locally advanced esophageal cancers.[4,5] In most trials, pCR rates from 20–30% have been achieved.[6-9]

Several trials have attempted to improve outcomes using different chemotherapy backbones with radiation therapy. The Sarah Cannon Research Institute reported a 41% 3-year survival with preoperative paclitaxel, carboplatin, infusional 5-FU, and concurrent radiation.[10] The addition of targeted agents to chemoradiation may further improve the efficacy of neoadjuvant treatment. Bevacizumab (Avastin, Genentech), a vascular endothelial growth factor (VEGF) inhibitor, improves the efficacy of combination chemotherapy in several diseases.[11-13] Preclinical data show that overexpression of VEGF confers a poor prognosis for esophageal cancer,[14] and that inhibitors of VEGF are radiosensitizers.[15] Overexpression of the epidermal growth factor receptor (EGFR) is seen in approximately 80% of patients with esophageal adenocarcinomas and squamous cell carcinomas.[16] EGFR overexpression is associated with poor prognosis for gastroesophageal cancer patients.[17,18] Erlotinib, an EGFR tyrosine kinase inhibitor, is also a potent radiosensitizer.[19] In this phase II trial, we evaluated the efficacy of bevacizumab and erlotinib when added to preoperative chemoradiation therapy with the Sarah Cannon regimen of paclitaxel, carboplatin, and infusional 5-FU in the treatment of localized cancers of the esophagus or esophageal junction. We hypothesized that the addition of bevacizumab and erlotinib to chemoradiation therapy would improve the pCR rate of treatment.

Patients and Methods

This open-label, nonrandomized phase II study was initiated in February 2007, and was performed at selected sites in the Sarah Cannon Research Institute Oncology Research Consortium (Appendix), a community-based clinical trials organization. The study was approved by the institutional review boards of all participating sites prior to study initiation.

Eligibility

Patients aged 18 years or older with previously untreated, histologically confirmed stage I, II, or III squamous cell, adenocarcinoma, or adenosquamous carcinoma of the esophagus or GE junction were eligible. Patients were required to be surgical candidates at enrollment, both in terms of location/stage and general medical condition. Additional eligibility criteria included Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; adequate organ and bone marrow function; measurable or evaluable disease by computed tomography (CT), positron emission tomography (PET) scan, or endoscopy; no metastatic disease; and no history of stroke, transient ischemic attack, cardiac infarction, or unstable angina in the 6 months prior to day 1 treatment.

Pretreatment Evaluation

Prior to beginning protocol therapy, all patients underwent a complete history and physical examination, determination of ECOG performance status, complete blood counts, comprehensive metabolic profile (including lactate dehydrogenase [LDH] and alanine transaminase [ALT]), blood pressure measurement, measurements of urine protein by dipstick or urine protein:creatinine (UPC) ratio, and serum pregnancy tests for women of childbearing potential. Patients also underwent an upper gastrointestinal (GI) endoscopy, an electrocardiogram, staging CT scans, and a PET scan.

Treatment

During the 6 weeks of preoperative treatment, all patients received paclitaxel (200 mg/m^2 IV), carboplatin (AUC 5.0 IV), and bevacizumab (15 mg/kg IV) on days 1 and 22. Patients took erlotinib 100 mg orally daily on days 1–42, and 5-FU was administered by continuous IV infusion (225 mg/m^2/day) on days 1–35. Radiation therapy was administered in 1.8-Gy single fractions, Monday–Friday, on days 1–35 (to a total of 45 Gy). Figure 1 details the treatment plan.

Following preoperative treatment, patients were re-evaluated during weeks 9–11. This re-evaluation included complete medical history and physical examination; complete blood count; comprehensive metabolic profile (including LDH and ALT); urinalysis or UPC ratio; upper GI endoscopy; restaging CT scans; and PET scan (for patients who had an abnormal baseline PET scan). Patients who were deemed candidates for surgical resection following this evaluation proceeded to surgery dur-

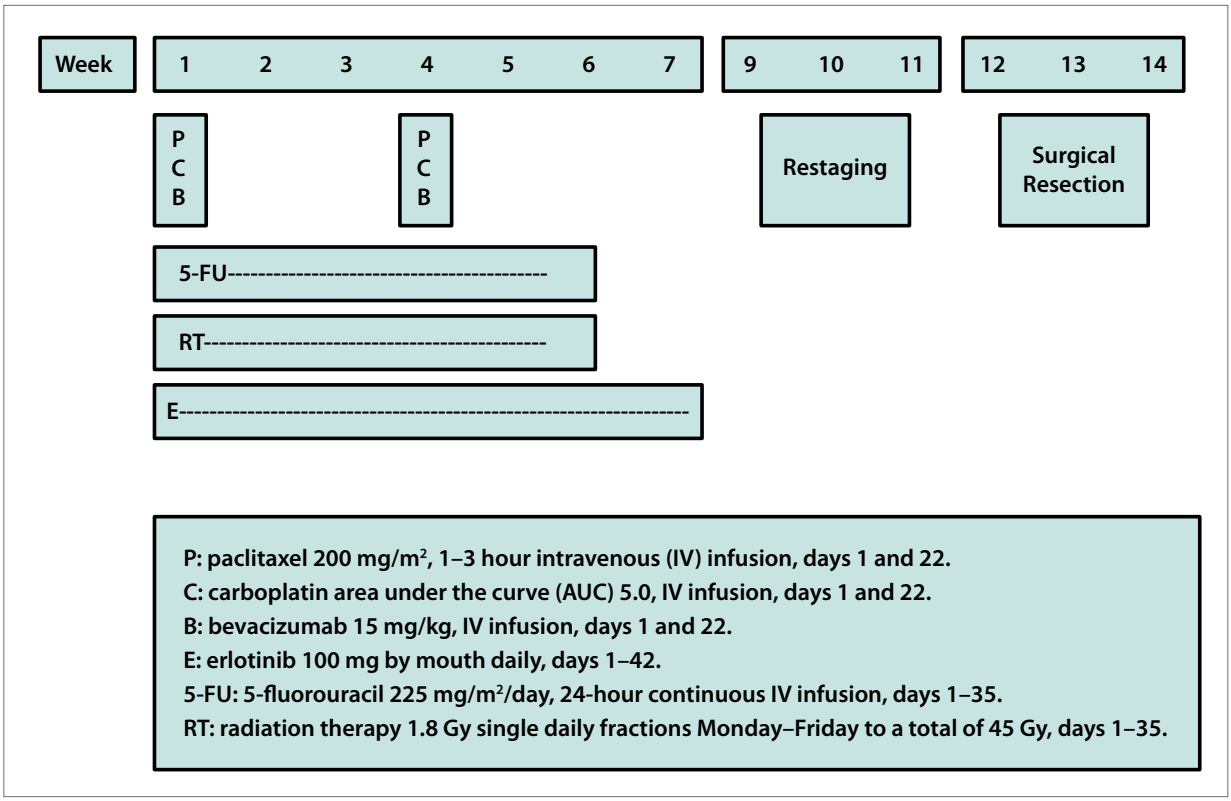

Figure 1. Treatment schedule.

ing weeks 12–14. Determination of candidacy for surgical resection, including disease status (worsened local disease or metastatic disease) and patient performance status, was performed in conjunction with the surgeon. Patients who were not deemed resection candidates at that time were removed from study participation and followed for progression and survival. Patients who were able to have a definitive surgical resection had no further protocol treatment administered following surgery, and were also followed for recurrence and survival.

Determination of Response to Treatment

Following the completion of neoadjuvant treatment, patients were assessed for clinical response to treatment using imaging studies with the following definitions: a complete clinical response was no residual tumor or mass on CT scan, PET scan, or upper GI endoscopy; and a partial clinical response was at least a 50% reduction in the size of all lesions, in the absence of new lesions.

For patients who went to surgical resection, pCR was defined as no residual viable cancer found at the primary site or regional lymph nodes upon pathologic review of the surgical specimen; and pathologic partial remission (pPR) was defined as an objective clinical response, but with residual viable tumor on surgical specimen. The pPR group was further subdivided into 2 categories, indicating microscopic or macroscopic residual disease in the surgical specimen. Stable disease was successful surgical resection, yet did not meet criteria for pCR or pPR. Patients with progressive disease were unable to undergo definitive surgical resection due to the extent of the tumor, or they had clear radiographic evidence of progressive disease prior to surgical resection.

Statistical Considerations

The primary endpoint in this trial was the pCR rate. Previous experience with neoadjuvant chemoradiation (without bevacizumab and erlotinib) yielded a pCR rate of approximately 40%, with a 3-year progression-free survival rate of 35%. An increase in the pCR rate from 40–60% would justify further study of this regimen. Enrollment of a total of 61 patients in this trial was required to document this change, with alpha and beta errors at 0.05 and 0.10, respectively.

The secondary endpoints of this trial included progression-free survival, overall survival, and an assessment of the tolerability and feasibility of this regimen. All patients who received at least 1 dose of treatment were included in the toxicity analysis.

Table 1. Patient Characteristics (N=62)

Characteristic	Number of Patients
Median age, years (range)	64 (43–76)
Sex	
Male	57 (92%)
Female	5 (8%)
Race	
Caucasian	60 (96%)
Black/African American	2 (4%)
ECOG performance status	
0	40 (65%)
1	22 (35%)
Histology	
Adenocarcinoma	58 (94%)
Squamous	4 (6%)
Location of primary	
Esophagus	31 (50%)
Upper thoracic	1 (2%)
Middle thoracic	1 (2%)
Lower thoracic	29 (46%)
GE junction	31 (50%)
Stage at enrollment	
I	1 (2%)
II	28 (45%)
III	30 (48%)
IVa	3 (5%)

ECOG=European Cooperative Oncology Group; GE=gastroesophageal.

In this trial, progression-free survival was defined as the interval from the date of first treatment until the date of disease progression or death, whichever occurred first. Patients who did not progress were censored at the date of their last tumor assessment. Overall survival was defined as the interval between the date of first treatment and the date of death. Patients who remained alive were censored at the date of their last tumor assessment. Progression-free and overall survivals were analyzed using the Kaplan-Meier method.

Results

Patient Characteristics

Between February 2007 and September 2009, 62 patients were enrolled (Table 1). The predominant histology was adenocarcinoma (94%); the majority of patients were Caucasian men (89%). Three patients (5%) with stage IVa disease (celiac involvement) were allowed on study.

Treatment Received

Forty-four of 62 patients (71%) completed neoadjuvant therapy and proceeded to surgical resection. Eighteen patients (16%) did not undergo surgical resection for the following reasons: treatment-related toxicity (6 patients); disease progression (6 patients, including 2 deaths due to progressive disease); patient request (4 patients); and patient noncompliance (1 patient). The treatment-related toxicities that resulted in study discontinuation were grade 3 dysphagia (2 patients), grade 4 colitis (1 patient), grade 3 GI bleeding (1 patient), declining performance status (1 patient), and grade 4 leukopenia (1 patient).

During neoadjuvant treatment, 51 patients (82%) received full-dose paclitaxel, and 49 patients (79%) received full-dose carboplatin. Five patients were removed from the study prior to receiving all doses; paclitaxel and carboplatin dosage was reduced in 6 patients, secondary to grade 3 mucositis/esophagitis, febrile neutropenia, and thrombocytopenia. Two patients received full-dose paclitaxel, but had carboplatin dose reductions due to increased creatinine. Thirty-two patients (52%) received the full dose of infusional 5-FU. Sixteen patients required dose reductions or interruptions of 5-FU due to grade 3 diarrhea, grade 3 rash, grade 3 mucositis/esophagitis, and grade 3 thrombocytopenia.

Erlotinib was administered at full dose in 33 patients (53%). Seventeen patients required dose interruption or early discontinuation of erlotinib due to grade 3 mucositis/esophagitis, grade 3 rash, grade 3 diarrhea, grade 4 febrile neutropenia, and grade 3 dehydration.

Bevacizumab was administered at full dose in 57 patients (92%). In addition to the 5 patients who were removed from the study prior to receiving all doses, bevacizumab dosing was delayed in 2 patients due to grade 3 mucositis/esophagitis.

A full dose of 45 Gy was administered to 45 patients (73%). Seventeen patients did not receive the full 45 Gy; radiation therapy was interrupted or discontinued due to toxicity in 10 patients (grade 4 neutropenia, 1 patient; grade 4 colitis, 1 patient; grade 3 mucositis/esophagitis, 4 patients; grade 3 odynophagia, 2 patients; grade 3 GI bleed, 1 patient; grade 3 dehydration, 1 patient). Four patients requested interruption in radiation therapy; 1 additional patient did not complete radiation therapy due to disease progression. Of the patients who did not receive full-dose radiation therapy, the median Gy delivered was 32.4 (range, 6.5–43.2).

Efficacy

Of the 44 patients who proceeded to surgical resection, surgical procedures were transhiatal esophagectomy (25 patients), Ivor-Lewis esophagogastrectomy (12 patients), radical esophagogastrectomy (4 patients), partial esophagogastrectomy (2 patients), and 3-hole esophagectomy (1 patient).

Table 2. Pathologic Responses to Treatment (N=62)

Pathologic Responses to Treatment	Number of Patients
Definitive resection performed Complete response Partial response	44 (71%) 18 (29%) 22 (35%)
Microscopic residual disease	18 (29%)
Macroscopic residual disease	4 (6%)
Stable disease	0
Unresectable at surgery	3 (5%)
No operation performed	15 (24%)

Eighteen patients (29%) were classified as having a pathologic complete remission at the time of surgery (Table 2). An additional 22 patients achieved a pPR (35%); 18 of these patients had microscopic residual disease, while 4 patients had macroscopic disease. At the time of resection, 3 patients were discovered to be inoperable, due to progression or previously unsuspected extent of disease. One additional patient who underwent a radical esophagogastrectomy was unable to have an R0 resection.

At a median follow-up of 32 months, the median progression-free survival (Figure 2) for this sample was 28.6 months (95% confidence interval [CI], 14.4–NR). Thirty-three patients (53%) remain alive; the median overall survival (Figure 3) was 30.2 months (95% CI, 19.4–NR).

Treatment-Related Toxicity

Treatment-related and postoperative grade 3/4 toxicities are outlined in Table 3. Myelosuppression was common, but only 1 patient discontinued study participation due to leukopenia. Common grade 3/4 nonhematologic toxicities included mucositis/stomatitis (42%), diarrhea (27%), and esophagitis (27%). There were 40 instances of hospitalization in 38 patients (61%) for toxicities believed to be related to treatment. The 40 treatment-related hospitalizations occurred due to the following: grade 2/3 dehydration (9 patients), grade 3/4 mucositis/esophagitis (8 patients), grade 3/4 febrile neutropenia (6 patients), grade 3 diarrhea (3 patients), grade 4 leukopenia (2 patients), grade 3 GI bleed (2 patients), grade 2/3 atrial fibrillation (2 patients), grade 4 abdominal evisceration (1 patient), grade 4 colitis (1 patient), grade 4 fatigue (1 patient), grade 3 malnutrition (1 patient), grade 3 nausea (2 patients), grade 3 peripheral artery ischemia (1 patient), and grade 3 syncope (1 patient). There were 2 postoperative deaths; 1 death was due to postoperative acute respiratory distress syndrome (ARDS), and the other death occurred in a patient who was found to be unresponsive, with no specific cause identified.

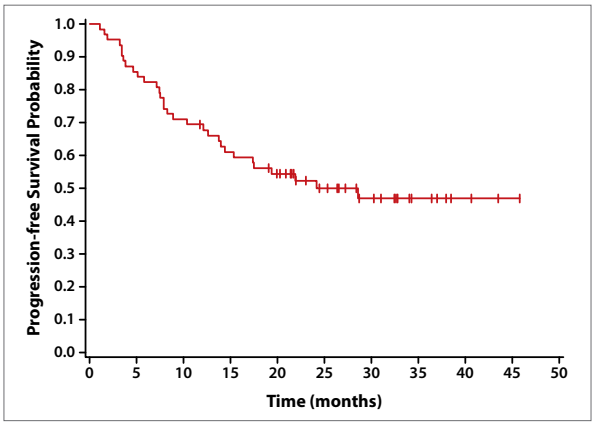

Figure 2. Progression-free survival (N=62).

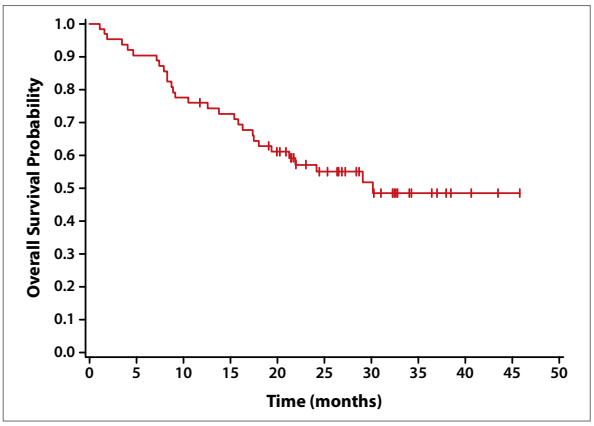

Figure 3. Overall survival (N=62).

Discussion

The optimal chemotherapy backbone in combination with radiation therapy for the neoadjuvant treatment of locally advanced esophageal cancer has not yet been determined. The most commonly used regimen is a combination of 5-FU plus cisplatin, which has shown pCR rates ranging from 25–40%,[8,20,21] median overall survivals in the 16–50-month range, and 3-year survival rates around 35%. Other trials have evaluated chemotherapy regimens that include cisplatin/paclitaxel, cisplatin/irinotecan, and 5-FU/oxaliplatin.[22-26] However, none of these trials have shown significant improvement over historic results with 5-FU and cisplatin. Three reported trials have evaluated the combination of paclitaxel, a platinum agent (carboplatin or cisplatin), and 5-FU with radiation therapy.[27-29] The largest of these was a multicenter trial of 123 patients with potentially resectable esophageal cancer.[29] The pCR rate was 30%, with a median progression-free survival of 19 months, a median overall survival of 22 months, and a 3-year overall survival of 41%. Grade

Table 3. Treatment-Related Toxicity (N=62) and Postoperative Toxicity (n=44)

	Number of Patients	
Neoadjuvant Toxicity	**Grade 3**	**Grade 4**
Hematologic		
Leukopenia	28 (45%)	12 (19%)
Neutropenia	17 (27%)	10 (17%)
Febrile neutropenia	6 (10%)	1 (2%)
Thrombocytopenia	2 (4%)	3 (5%)
Anemia	3 (5%)	1 (2%)
Nonhematologic		
Mucositis/stomatitis	24 (39%)	2 (4%)
Dehydration	19 (32%)	0
Diarrhea	17 (27%)	0
Esophagitis	16 (26%)	1 (2%)
Anorexia	10 (16%)	0
Fatigue	8 (13%)	1 (2%)
Rash/desquamation	7 (10%)	2 (4%)
Nausea/vomiting	4 (7%)	0
GI bleeding	3 (5%)	0
Thrombus/embolism	3 (5%)	1 (2%)
Peripheral artery ischemia	1 (2%)	0
Syncope	1 (2%)	0
Wound complication	0	2 (4%)
Abdominal evisceration	0	1 (2%)
Postoperative Toxicity	**Grade 3**	**Grade 4**
Ascites	1 (2%)	0
Infection	1 (2%)	0
Cardiopulmonary arrest	0	1 (2%)
Pleural effusion	1 (2%)	0
Respiratory distress	0	1 (2%)

GI=gastrointestinal.

3/4 toxicities included leukopenia (73%), fever and neutropenia (22%), esophagitis/mucositis (43%), nausea/vomiting (16%), and diarrhea (10%).

Based on these encouraging data, this current trial of paclitaxel, carboplatin, and 5-FU plus 2 promising targeted agents was undertaken. In other cancers, the VEGF inhibitor bevacizumab improves outcomes when combined with chemotherapy,[11-13] and has preclinical evidence of being a radiosensitizer.[15] In patients with metastatic esophagogastric cancers, bevacizumab in combination with various chemotherapy regimens showed improvements in response rates, median progression-free survival, and median overall survival when compared to historic controls.[30-32] However, a recent press release of the AVAGAST (Avastin in Gastric Cancer) trial, a randomized phase III trial comparing chemotherapy with or without bevacizumab in patients with metastatic gastric cancer, stated that the trial failed to meet its primary endpoint of overall survival. Erlotinib, an EGFR tyrosine kinase inhibitor, is also a known radiosensitizer.[19] Trials of erlotinib in esophagogastric adenocarcinomas show response rates ranging from 0–9%.[33,34] With the radiosensitizing potential of these agents, as well as potential antitumor activity, bevacizumab and erlotinib were combined with chemoradiation therapy.

The combination of paclitaxel, carboplatin, 5-FU, bevacizumab, erlotinib, and radiation therapy resulted in a pCR rate of 29%, median progression-free survival of 28.6 months, and median overall survival of 30.2 months. These results are similar to those obtained in previous trials, including the large phase II study of the same chemotherapy regimen (paclitaxel, carboplatin, and 5-FU) in combination with radiation therapy.[29] Interestingly, the largest proportion of patients in this trial had adenocarcinomas (94%), compared to the previous phase II experience, where 71% of patients had adenocarcinomas. In the previous phase II study, patients with adenocarcinomas had a lower rate of pCR compared to squamous cell carcinomas (37% vs 53%, respectively). This demographic difference may have contributed to the slightly lower complete response rate seen in the current study.

Bevacizumab in combination with cisplatin, irinotecan, and radiation therapy for localized esophageal adenocarcinomas is being studied in another clinical trial.[35] So far, this trial has accrued 18 patients, with 1 of 10 patients having a pCR. The toxicities seen to this point are not significantly increased compared to historic toxicities, and the trial accrual continues. Several EGFR-targeted agents have been studied with chemoradiation for localized esophageal cancers. A phase II study of gefitinib plus 5-FU, cisplatin, and radiation therapy enrolled 37 patients with localized esophageal cancer, primarily squamous cell.[36] The pCR rate was 25%, but was well tolerated, with diarrhea and rash of mostly grade 1/2. A smaller trial of gefitinib with paclitaxel, cisplatin, and radiation therapy enrolled 17 patients with adenocarcinomas.[37] The pCR rate was 18%, with a median time-to-progression of 16.4 months, and a median overall survival of 31.5 months. Like the previous phase

II study, the regimen was tolerable, and there were no significant increases in side effects over chemoradiation. Cetuximab (Erbitux, ImClone) plus chemoradiation has been examined in several small studies.[38-40] These studies show general feasibility of cetuximab-based chemoradiation therapy. Cetuximab is currently being studied in the Radiation Therapy Oncology Group's RTOG 0436 trial as a component of definitive chemoradiation therapy for locally advanced esophageal cancer.

Compared to the previous phase II study of paclitaxel, carboplatin, and 5-FU, the rates of grade 3/4 hematologic toxicity were similar, and included leukopenia (64%), thrombocytopenia (9%), and febrile neutropenia (12%). Nonhematologic toxicity also appeared similar, except for toxicities due to the targeted therapies, such as diarrhea (27%) and rash (14%). In lung cancer, bevacizumab in conjunction with radiation therapy has been associated with an increased risk of tracheoesophageal fistula formation.[41] However, no cases were seen in this trial, possibly due to the lower radiation dose administered. Other severe toxicities possibly related to bevacizumab were also uncommon, including 1 postoperative wound complication, 4 thromboembolic events, and 3 grade 3 GI bleeds. The rate of esophagitis did not increase significantly. Seventy-one percent of patients were able to complete neoadjuvant therapy, with most patients receiving at or near full-dose treatment. Two patients died postoperatively, 1 of ARDS, and 1 of unknown cause, giving a 4.5% operative mortality rate, which is not significantly increased compared to other combined modality regimens. Sixty-one percent of patients required hospitalization due to treatment-related toxicity.

This combination of chemotherapy, targeted therapy, and radiation therapy did not show any significant improvement in pCR rate or survival when compared to other neoadjuvant chemoradiation regimens. The rates of toxicity were not markedly increased compared to other neoadjuvant studies in esophageal cancer, but did show some targeted agent–specific toxicities. Since no improvement in efficacy was suggested, further study of this multi-agent regimen is not planned.

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Appendix

Sarah Cannon Research Institute Participating Sites

Tennessee Oncology, PLLC
Nashville, Tennessee

Oncology Hematology Care
Cincinnati, Ohio

Florida Cancer Specialists
Fort Myers, Florida

Consultants in Blood Disorders and Cancer
Louisville, Kentucky

Integrated Community Oncology Network
Jacksonville, Florida

Chattanooga Oncology Hematology Associates
Chattanooga, Tennessee

Hematology Oncology Associates of Northern NJ
Morristown, New Jersey

Aultman Health Foundation
Canton, Ohio