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Gastrointestinal Cancer

Phase II Study of Preoperative Chemoradiotherapy with Oxaliplatin, Infusional 5-Fluorouracil, and Cetuximab Followed by Postoperative Docetaxel and Cetuximab in Patients with Adenocarcinoma of the Esophagus: A Trial of the ECOG-ACRIN Cancer Research Group (E2205)

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Esophageal adenocarcinoma • Chemoradiotherapy • Cetuximab

Abstract

Background. A standard approach to treating resectable esophageal adenocarcinoma is chemoradiotherapy (CRT) followed by surgery; however, recurrence is common. To improve this, we designed a single-arm, phase II trial that added an epidermal growth factor receptor (EGFR) inhibitor, cetuximab (C), to CRT, with the hypothesis that EGFR inhibition would improve pathologic complete response (pCR) rate.

Materials and Methods. We aimed to increase the pCR rate from 25% to 45%. A Simon two-stage design (α and β of 0.10) required pCR/enrolled 5/18 for stage 1 and 14/40 total. CRT: oxaliplatin 85 mg/m^2 days 1, 15, and 29; infusional 5-fluorouracil 180 mg/m^2/24 hours × 35 days; C 400 mg/m^2 day 1 then 250 mg/m^2 days 8, 15, 22, and 29 and radiation (intensity modulated radiotherapy [IMRT] allowed) 180 cGy/day × 25 fractions (Monday through Friday). Following esophagectomy, adjuvant chemotherapy (CT): weekly docetaxel 35 mg/m^2 and C 250 mg/m^2 5 out of 6 weeks for two cycles.

Results. Of 21 eligible patients enrolled, 17 had surgery; 4 died before operation (due to pulmonary embolism 4 days after CRT, G3 diarrhea, progressive disease during CRT, sepsis/hypoxia during CRT, and acute respiratory distress syndrome [ARDS]). pCR = 7/17. Three postoperative deaths due to ARDS resulted in seven total study-related deaths. Of the 14 remaining patients, 12 started and completed adjuvant CT. Two of seven patients with pCR died, both of ARDS. Out of the 21 eligible subjects in this study, 13 have died and 8 remain alive. The use of IMRT did not correlate with ARDS.

Conclusion. This regimen demonstrated promising activity. Toxicity was significant, with seven study-related deaths leading to closure after stage 1. All postoperative deaths were due to ARDS. This regimen is not recommended. ***The Oncologist*** 2020;25:e53–e59

Implications for Practice: Esophageal cancer is a disease with a high death rate. The current treatment involves giving chemotherapy plus radiation followed by surgery, but this cures only a quarter of patients. In order to improve survival, better treatments are needed. This trial evaluated the addition of a novel drug, cetuximab, to chemotherapy plus radiation. Unfortunately, the side effects were too great and the study was stopped early.

Introduction

Esophageal adenocarcinoma is an epithelial tumor in which the epidermal growth factor receptor (EGFR) is overexpressed in approximately 30%–70% of cases and for which improved prognostic methods and therapies are needed [1, 2]. Although

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it makes up a small percentage (1.5%) and low incidence (14,000) of total cancer cases in the U.S., mortality remains high [3]. Locally advanced, nonmetastatic disease is curable in up to 40%–45% of patients when multimodality therapy is used [4].

Preoperative chemoradiotherapy (CRT) increases survival versus surgery alone in patients with adenocarcinoma. The CALGB 9780 study randomized 56 patients with esophageal or gastroesophageal junction adenocarcinoma to either surgery alone or surgery after CRT with cisplatin and 5-fluorouracil (5-FU). Five-year survival was 39% (95% confidence interval [CI], 21%–57%) versus 16% (95% CI, 5%–33%) in favor of preoperative CRT [5]. The more recently reported CROSS trial randomized 400 patients with gastroesophageal cancer (75% adenocarcinoma) to preoperative CRT with carboplatin and paclitaxel versus surgery alone [6]. In the long-term results after a minimum follow-up of 5 years, survival in the cohort with adenocarcinoma was significantly better in the combined modality arm (43.2 months [24.9–61.4] vs. 27.1 months [13.0–41.2]; hazard ratio [HR], 0.73 [95% CI, 0.55–0.98]; log-rank p = .038]) [7]. However, neither trial included adjuvant chemotherapy or targeted therapy, and overall survival (OS) did not exceed 50%. Additional safe and effective CRT combinations have been studied in phase II trials, in particular one that substitutes oxaliplatin for cisplatin [8].

Another validated approach for treatment of locally advanced, resectable gastric and gastroesophageal junction (GEJ) adenocarcinoma was reported in the FLOT4-AIO study. These data apply to our study given that 41% of these patients also had GEJ adenocarcinoma. In summary, perioperative treatment with Arbeitsgemeinschaft Internistische Onkologie (AIO) versus epirubicin, cisplatin, 5-FU (ECF) resulted in a significantly greater fraction of pathologic responders [9], further supporting the benefit of neo-adjuvant treatment in this population. Differences in treatment compared with this study included the absence of preoperative radiation and much higher fraction of patients receiving adjuvant chemotherapy.

Postoperative chemotherapy is another approach, although infrequently studied, to increase survival versus surgery alone. The phase II E8296 trial evaluated adjuvant cisplatin (75 mg/m^2) and paclitaxel (175 mg/m^2 over 3 hours) every 3 weeks for four courses in patients with completely resected, node-positive adenocarcinoma of the esophagus, GEJ, and gastric cardia. After a median follow-up of 2.9 years (minimum follow-up of 2 years), the actuarial 2-year survival rate was 60% [10]. The Japan Clinical Oncology Group evaluated postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus, but this was limited to squamous cell cancer [11].

Current knowledge about the molecular mechanisms of cancer-related pathways involved in cellular signaling, cell cycle regulation, cell death, and angiogenesis is yielding effective therapies directed at specific components of these pathways. The EGFR is a target of several drugs, including the small molecules gefitinib and erlotinib as well as the monoclonal antibodies cetuximab and panitumumab. The EGFR is a prognostic factor and a target for therapy with anti-EGFR monoclonal antibodies in a number of epithelial malignancies including head and neck squamous cell cancer and colorectal cancer [12, 13]. In addition, overexpression of the EGFR in patients with esophageal adenocarcinoma (EAC) treated with preoperative CRT correlates with worse outcome [2].

With the goal of improving efficacy without increasing toxicity in this patient population, we incorporated the anti-EGFR monoclonal antibody, cetuximab, into preoperative CRT for patients with locally advanced, resectable EAC. An oxaliplatin/5-fluorouracil chemotherapy backbone was chosen based on the regimen developed by Khushulani and colleagues, which has been further evaluated in more contemporary studies [8, 14]. In addition, we evaluated the safety and tolerability of the combination of cetuximab and docetaxel given weekly postoperatively to this group of patients already pretreated with CRT and surgery. Docetaxel was chosen based upon its activity against EAC as well as a potential or inhibiting angiogenesis [15–17]. Secondary objectives also included exploratory studies to determine if this regimen's activity correlates with EGFR-related genetic and pathway activation markers and circulating endothelial and tumor cells—to be reported elsewhere.

Materials and Methods

Eligibility Criteria

Eligible patients >18 years of age must have had newly diagnosed biopsy-proven adenocarcinoma of the esophagus stages (American Joint Committee on Cancer 6th edition) T2N0M0, T3N0M0, T1-3N+M0, or T1-3N0-1M1a as determined by imaging studies (positron emission tomography/computed tomography, endoscopic ultrasound) performed less than 4 weeks prior to registration, with no greater than 2 cm extension into the cardia. Patient tumors must be considered surgically resectable (not T4). Patients with a history of a curatively treated malignancy must have been disease-free for at least 2 years and have a survival prognosis that is greater than 5 years. Performance status by Eastern Cooperative Oncology Group (ECOG) 0–1, normal laboratory and organ functions, and no acute intercurrent illness were required. Women of childbearing potential were excluded.

The trial was reviewed and approved by the institutional review board at each participating institution.

Treatment

Preoperative therapy consisted of the following: oxaliplatin 85 mg/m^2 over 120 minutes intravenously (IV) days 1, 15, 29; cetuximab initial dose 400 mg/m^2 over 120 minutes day 1 and subsequent doses 250 mg/m^2 over 60 minutes IV days 8, 15, 22, 29; and 5-FU 180 mg/m^2 continuous infusion IV over 24 hours days 1–35.

Radiation was as follows: computed tomography-based planning was required. External beam radiotherapy (RT) with megavoltage linear accelerator was given 5 days per week at 180 cGy per day to a total dose of 45 Gy. All fields were treated each day, and portal films were obtained of at least two fields per week or more often if needed. Treatment was given with a combination of anterior/posterior, posterior oblique, or lateral fields, such that the dose to the target

volume met the required uniformity criteria. Parallel opposed oblique fields could not be used for the entire course. If a three-field technique was used, all three fields were treated daily. The patient treatment position was either supine or prone (which may allow a shift in the esophagus in cases in which sparing of the spinal cord is difficult). Simulation on a diagnostic quality RT simulator or computed tomography simulator was required. In accordance with current guidelines for use of IMRT in clinical trials (see www.QARC.org), IMRT was used only if the degree of tumor motion was assessed and could be limited to 1.0 cm. If required to achieve this goal, techniques for managing or suppressing tumor motion were applied.

Surgery occurred between 28 and 56 days after completion of preoperative CRT. Patients underwent a history, physical exam, and computed tomography of the chest and upper abdomen within 2 weeks prior to surgery to rule out evidence of distant disease or unresectability. Choice of type of resection (Ivor-Lewis, transhiatal, etc.) was left to the operating surgeon. One field lymph node dissection was required. A microscopic proximal or distal margin of <1 mm was considered positive. Proximal and distal margins were at least 2 cm beyond gross tumor as measured in the operating room after removal of the esophagus but prior to fixation of the specimen. Frozen sections were obtained to ensure microscopically negative proximal and distal margins.

Postoperative therapy was administered only to patients who had an R0 or R1 resection. It was started after recovery from surgery (28–56 days) and no later than day 56 postoperatively. Docetaxel 35 mg/m^2 was given over 60 minutes IV once per week for 5 weeks out of 6 along with cetuximab initial dose 400 mg/m^2 over 120 minutes day 1 and subsequent doses 250 mg/m^2 over 60 minutes IV weekly for a total of 11 doses. Two cycles of 6 weeks each were given.

Dose Modifications

All toxicities were graded according to the Common Terminology Criteria for Adverse Events (version 3.0).

If treatment was interrupted for 4 consecutive weeks, protocol treatment was discontinued.

In addition to treatment delays, all drugs could be dose reduced as follows. Oxaliplatin could be dose reduced two levels (65 mg/m^2 and 50 mg/m^2) based on extent of neurologic, pulmonary, and hematologic events. Fluorouracil could be dose reduced two levels (135 mg/m^2 and 90 mg/m^2) for mainly gastrointestinal, oral-mucosal, and palmar-plantar toxicities. The continuous 5-FU was not interrupted. Cetuximab could be reduced two levels (200 mg/m^2 and 150 mg/m^2) for skin and pulmonary toxicities. Infusion reactions were managed per package insert guidelines. Docetaxel could be reduced two levels (28 mg/m^2 and 22 mg/m^2) mainly for hematologic, neurologic, stomatitis, and elevation of bilirubin toxicities.

There were to be no radiation dose modifications. Radiotherapy could be interrupted for grade >3 radiotherapy-related toxicity except for grade 3 esophagitis and skin reaction, which were managed with supportive care. Treatment resumed when toxicity resolved to grade 2. For grade 4 toxicity requiring hospitalization (even if unrelated to radiotherapy), the treatment could be interrupted at the discretion of the treating physician. If radiation therapy was interrupted, 5-FU infusion continued, and if radiation extended past 35 days, the 5-FU infusion continued until radiation was completed.

Response Criteria

A pathologic complete response (pCR) was the absence of any histopathologic evidence of tumor in the resected esophageal and nodal tissues.

A pathologic incomplete response was defined as the presence of histopathologic evidence of any tumor in the resected esophageal and/or nodal tissues.

Overall survival was measured from the date of registration to the date of death. Patients lost to follow-up were censored for survival analysis.

Study Design and Statistical Methods

This study had a two-stage design [18]. At the initial stage, 19 patients would be entered, with an assumption that 18 of those patients would be eligible. If at least five responses were observed among the first 18 eligible patients, 23 additional patients would then be entered (with the assumption that 22 would be eligible). Eligible patients would then total to 40. If at least 14 responses were observed among the first 40 eligible patients, the treatment would be considered promising. Estimated accrual was at 30 patients per year.

A complete response rate of 45% or more was defined as evidence of activity. The study had at least 90% power against the null of 25% complete response rate with a one-sided significance level of 0.10.

Toxicity was a secondary endpoint. The design had a 34% chance of at least one grade 3 or higher toxicity for all 42 patients accrued if the true complication rate was 1%, and an 88% chance of at least one complication if the true complication rate was 5%. With 42 patients total, a 90% confidence interval for the true but unknown rate of complication would be no wider than 27%.

Therapy was to be discontinued for any of the following reasons: treatment interruption for 4 consecutive weeks, extraordinary medical circumstances, progressive disease, disease recurrence, R2 resection, unacceptable toxicity, or patient choice.

All patients (including those who discontinued early from protocol therapy) were followed until progression and/or death, for 2 years from date of registration at every 3 months, and then another 3–5 years at every 6 months.

Data lock occurred November 10, 2011.

Results

This study was activated on June 10, 2008, suspended on April 10, 2009, and terminated on January 8, 2010, with a final accrual of 22 subjects (1 ineligible). The ineligible subject had an initial pathologic diagnosis of esophageal adenocarcinoma; however, after resection, the final pathology was gastric (fundus) adenocarcinoma with superior extension into the cardia.

Patient Characteristics

Table 1 displays patient demographics at baseline of the 21 eligible patients. The median age was 62 years (range 45–79 years). All 21 patients were white, and 19 (90%) were male. Esophagus primary site was distributed as follows:

Table 1. Patient characteristics (n = 22)

Characteristics	*n* (%)
Sex	
Male	20 (90.9)
Female	2 (9.1)
Age, years	
≤65	15 (68.2)
>65	7 (31.8)
Race	
White	22 (100.0)
Ethnicity	
Missing/unknown	1 (4.5)
Non-Hispanic	21 (95.5)
PS	
0	17 (77.3)
1	5 (22.7)
Stage	
T2N0M0 or T3N0M0	6 (27.3)
T1-3N+M0 or T1-3N0-1M1A	16 (72.7)
Site	
Esophagus	12 (54.5)
GEJ	10 (45.5)
Differentiation	
Moderate, grade 2	4 (18.2)
Poor, grade 3	18 (81.8)

Abbreviations: GEJ, gastroesophageal junction; PS, performance status.

one subject (4.8%) mid-thoracic, nine (42.9%) lower thoracic, nine (42.9%) GEJ, and two (9.5%) esophagus not otherwise specified.

Treatment Received

Preoperative Chemotherapy

All 21 eligible subjects started on preoperative treatment with oxaliplatin, 5-FU, cetuximab, and radiation; however, 1 patient did not receive oxaliplatin, 5-FU, or radiation. Multiple subjects had dose modifications or missed doses during the preoperative treatment: oxaliplatin (n = 12), 5-FU (n = 1), and cetuximab (n = 21). For cetuximab, all subjects experienced a dose modification from day 1 of treatment (mean of 791.4 mg daily) to day 8 (mean of 515.9 mg daily). Reasons for dose modifications included hematologic, diarrhea, hypotension, hypomagnesemia, fatigue, hypotension, and the fatal events listed below.

Four patients did not go to surgery because of cetuximab reaction, death from pulmonary embolism 4 days after CRT, G3 diarrhea during CRT, and death from sepsis/hypoxia during CRT. Two deaths occurred during the preoperative treatment.

Radiation

Twelve patients received conventional (standard radiation), and eight received conformal (IMRT). Median dose was 4,500 cGy. Interruptions to radiation were experienced by eight subjects. There was no correlation between pulmonary toxicity (acute respiratory distress syndrome [ARDS]) and radiation modality. The small numbers of patients with ARDS preclude a robust comparison of this event with radiation dose parameters, but descriptive results do not suggest an association. The median proportion of volume of lung receiving 5 Gy and 20 Gy for those with and without ARDS was 60% (46%–72%) versus 50% (17%–78%), and for volume receiving 20 Gy, the proportion was 17% (17%–19%) versus 11% (5%–30%).

Table 2. Perioperative deaths

Patient	Cause of death
22001	Died after resection of ARDS
22005	Died after resection of ARDS
22009	Died 4 days after completing CRT of pulmonary embolus
22010	Died of pneumonia/disease progression preoperatively, after only completing 18 days of CRT
22012	Died of cardiac arrest 34 days after completion of CRT. Had grade 4 ARDS before death
22013	Died of ARDS. Did not receive full preoperative chemotherapy but received full-course RT
22019	Died prior to completing CRT of sepsis and hypoxia

Abbreviations: ARDS, acute respiratory distress syndrome; CRT, chemoradiotherapy; RT, radiotherapy.

Surgery

Perioperative events that occurred in the 17 patients who underwent resection included pneumonia (two instances), arrhythmia (two instances), and vocal cord palsy (three instances—all three documented by laryngoscopy). In addition, there were three postoperative deaths from ARDS.

During surgery, tumor extent (extent of invasion) was assessed for five different areas: trachea, pericardium, diaphragm, major blood vessel, and pleura/lung. Among the 17 subjects who underwent surgery, none of these areas were involved. All 17 subjects had negative proximal and distal margins. Two had unknown lateral/deep margins, whereas 16 were negative. Adventitial margins were unknown in four and negative in the remainder.

The pathologic completed response rate was 7/17 (41%). patients who underwent surgery and 7/21 (33%) for the intention-to-treat population.

Postoperative Chemotherapy

Of the 14 patients remaining alive after surgery, 12 started and completed postoperative treatment. Docetaxel was generally well tolerated, with only a few weekly doses held. For cetuximab, a large adjustment in dosing occurred between weeks 1 and 2, lowering the average dose from 786.92 mg in week 1 to 490.85 mg in week 2. Once the dose stabilized, few more were missed. No subjects reported nonprotocol therapy, in either cycle 1 or cycle 2.

Recurrence and Survival

As of November 2011 analysis of 21 eligible subjects, 9 recurred (of 14 alive after surgery): 5 distant only, 2 local only, and 2 both. Of these nine, six received postoperative treatment. Causes of death were as follows: treatment complications (see toxicity) and disease recurrence and unknown.

Table 3. Toxicity summary

	Treatment arm A (n = 22), n		
	Grade		
Toxicity type	**3**	**4**	**5**
Allergic reaction	—	1	—
Hemoglobin	4	—	—
Leukocytes	2	—	—
Lymphopenia	3	2	—
Neutrophils	1	—	—
Platelets	—	2	—
Heart block asystole	—	1	—
Atrial fibrillation	—	1	—
Cardiac troponin I	1	—	—
Hypotension	1	1	—
Fatigue	4	1	—
Weight loss	1	—	—
PTT	1	—	—
Thrombotic microangiopathy	—	1	—
Coagulation—other	1	1	—
Alopecia	1	—	—
Rash/desquamation	1	—	—
Rash: acne/acneiform	1	—	—
Radiation dermatitis	1	—	—
Death—multiorgan failure	—	—	1
Anorexia	5	—	—
Constipation	1	—	—
Dehydration	8	—	—
Diarrhea without prior colostomy	4	—	—
Distention/bloating, abdominal	1	—	—
Dysphagia	3	—	—
Esophagitis	5	—	—
Malabsorption	1	—	—
Mucositis/stomatitis (symptom) esophagus	3	—	—
Nausea	5	—	—
Necrosis, small bowel NOS	—	1	—
Perforation, colon	1	—	—
Stenosis (including anastomotic) esophagus	1	—	—
Vomiting	2	—	—
Surgical hemorrhage	—	1	—
Infection grade 0–2 neutropenia, brain	—	1	—
Infection grade 0–2 neutropenia, colon	1	—	—
Infection grade 0–2 neutropenia, lung	—	1	—
Infection grade 0–2 neutropenia, small bowel	—	1	—
Infection with unknown ANC wound	2	—	—
Infection grade 0–2 neutropenia, blood	—	1	1
Hypoalbuminemia	3	—	—
Alkaline phosphatase	1	—	—
Hypocalcemia	4	—	—
Hyperglycemia	1	—	—
Hypomagnesemia	—	1	—
Hypophosphatemia	1	—	—
Hypokalemia	2	—	—
Hyponatremia	2	—	—
Nonneuropathic generalized weakness	1	—	—
Laryngeal nerve dysfunction	1	—	—
Neuropathy-motor	—	1	—
Depressed level of consciousness	—	1	—
Syncope	1	—	—
Abdomen, pain	1	—	—
Esophagus, pain	1	—	—
ARDS	—	1	4
Dyspnea	2	—	—
Hiccoughs	1	—	—
Hypoxia	—	4	—
Pleural effusion (nonmalignant)	1	1	—
Pneumonitis/pulmonary infiltrates	1	1	—
Pulmonary/upper respiratory—other	1	—	—
Vascular access, thrombosis/embolism	—	1	—
Thrombosis/thrombus/embolism	—	2	1
Worst degree	7	6	6

Grade 3 or higher adverse events.

Abbreviations: ANC, absolute neutrophil count; ARDS, acute respiratory distress syndrome; NOS, not otherwise specified; PTT, partial thromboplastin time.

Out of the 21 eligible subjects in this study, 13 have died and 8 remain alive.

Toxicity

Seven subjects died on treatment, either preoperatively (n = 4) or shortly after surgery (n = 3; Table 2), of ARDS, pulmonary embolism, pneumonia, and sepsis.

A summary of grade 3 or higher treatment-related adverse events is given in Table 3 (counts, out of all 22 treated patients). Six patients (22001, 22005, 22009, 22012, 22013, and 22019) were reported as having grade 5 events (three

ARDS, one infection, one thrombosis/embolism, and one multiorgan failure). Of note, in addition to other reported grade 4 events, there was one ARDS reported (case 22012).

Discussion

We designed this trial in an attempt to improve upon the modest survival results achieved with preoperative CRT using cytotoxic drugs. At the time that this study was designed, the most commonly used drugs were cisplatin and 5-fluorouracil. Concurrent CRT in the Radiation Therapy Oncology Group (RTOG) 85-01 [19] and Intergroup 0123 trials [20] demonstrated the superiority of the CRT versus surgery alone as definitive therapy for locally advanced disease. The benefit of radiosensitization was studied preoperatively with the goal of downstaging disease, facilitating surgery, and increasing survival. An update of these approaches substituted cisplatin/5-FU with FOLFOX [8]. In this study by Khushulani and colleagues, oxaliplatin with continuous-infusion 5-FU achieved similar efficacy with lower toxicity.

In order to improve the survival for patients with resectable esophageal adenocarcinoma, one must improve both local and distant control. To achieve this goal, we designed a single-arm, phase II study of the addition of cetuximab to preoperative CRT and postoperative chemotherapy in patients with locally advanced, resectable esophageal adenocarcinoma. The primary efficacy endpoint was pathologic response, with a two-stage design to account for early assessment of safety and toxicity. Although the study nearly met the endpoint of a pCR of 45%, toxicity was the major take-home message. A total of 9 of the 15 patients who underwent surgery recurred, 4 of these locally. This is in contrast to the experience reported in the SAKK trial, in which there were fewer local recurrences [21].

Unexpectedly, significant pulmonary toxicity occurred. Of 21 patients entered and treated on the study, 7 died during the pre- or immediately postoperative period. Of particular concern were the four deaths from ARDS. The study was stopped early because of these grade 5 events, the cause of which remains unknown. Several etiologies have been proposed. One concern was the interaction between IMRT and the preoperative regimen. However, we reviewed the QARQ data extensively and did not find a correlation between patients receiving IMRT (n = 8) and conventional (n = 12) approaches. In addition, in the 86-patient predecessor trial, ECOG 1201, that gave neoadjuvant chemoradiotherapy along with paclitaxel/cisplatin or irinotecan/cisplatin chemotherapy, no ARDS cases occurred [22]. Remarkably, for the 15 patients in E2205 who received radiation that met the dosing criteria of E1201, there were 3 cases of ARDS. With the possibility of radiation delivery anomalies as a causative factor being less likely, we turned to the theory that addition of cetuximab to CRT was the culprit.

Pulmonary toxicity of cetuximab is rare (package insert, [23]), occurring in <0.5% of patients treated with cetuximab alone or with chemotherapy. When given concurrently with radiation, in general, there is no increase in pulmonary adverse events, such as pneumonitis or ARDS. The RTOG 0617 trial, for example, evaluated standard-dose versus high-dose conformal radiotherapy with concurrent chemotherapy and the addition of cetuximab to concurrent chemoradiation for patients with inoperable stage III non-small cell lung cancer [24]. There was no difference in pulmonary toxicity between arms.

RTOG 0436 used a similar approach for the treatment of locally advanced squamous cell and adenocarcinoma of the esophagus [25]. Cisplatin and paclitaxel with or without cetuximab yielded no difference in pulmonary toxicity. The SAKK trial also studied the addition of cetuximab to preoperative CRT (cisplatin and docetaxel). There were no treatment-related deaths in the cetuximab arm, and OS with cetuximab versus control was 5.1 years (95% CI, 3.7 to not reached) versus 3.0 years (95% CI, 2.2–4.2) for cetuximab and control, respectively (HR, 0.73; 95% CI, 0.52–1.01; p = .055) [21]. Other agents used concurrently with CRT and known to cause pulmonary toxicity include gemcitabine, taxanes, anthracyclines, bleomycin, tyrosine kinase inhibitors, and immune checkpoint inhibitors [26].

Regarding the use of epidermal growth factor receptor antagonists in esophageal cancer, many studies have been done but do not show benefit, with the exception of the SAKK trial. RTOG 0436, which was definitive treatment without surgery, was a negative trial for efficacy. In SCOPE1, also a nonsurgical trial, 258 patients were randomized to receive CRT alone or CRT with cetuximab, and the cetuximab arm did worse [27].

In the setting of advanced/metastatic disease, the results are similar. The REAL-3 trial evaluated the addition of panitumumab to epirubicin, oxaliplatin, and capecitabine for first-line treatment of esophagogastric cancer and reported no difference in survival [28]. The EXPAND trial added cetuximab to cisplatin and capecitabine, with similar results [29]. Several studies evaluating the addition of anti-EGFR tyrosine kinase inhibitors also did not show benefit.

Conclusion

This study evaluated the addition of cetuximab to chemoradiation followed by surgery for locally advanced esophageal adenocarcinoma. It was stopped early because of significant and severe pulmonary toxicity of an unknown cause. Given this toxicity as well as other data showing lack of efficacy of epidermal growth factor receptor inhibition in this disease, cetuximab cannot be recommended in this setting.

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Disclosures

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