A Phase I Study of Concurrent Chemoradiotherapy and Cetuximab for Locally Advanced Esophageal Cancer

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Abstract. Aim: To determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of concurrent chemoradiotherapy and cetuximab in patients with non-resectable locally advanced esophageal cancer. Patients and Methods: Escalating doses of oxaliplatin every second week and daily tegafur/uracil were given concurrently with radiotherapy, 59.4 Gy in 33 fractions. Cetuximab was given on day 15 (400 mg/m²) and weekly (250 mg/m²) during radiotherapy. Fixed doses of oxaliplatin (130 mg/m²) and tegafur/uracil (300 mg/m²) were administered before, and after radiotherapy. Results: Eleven patients were included in the study; two were excluded due to allergic reactions to cetuximab. In DL2 (tegafur/uracil 300 mg/m², oxaliplatin 30 mg/m²) two grade 3/4 fistula and one grade 3 neuropathy were observed. Six patients were enrolled in DL1 (tegafur/uracil 150 mg/m², oxaliplatin 30 mg/m²) with no DLTs. Four out of 9 patients had complete response. Conclusion: Concomitant chemoradiotherapy and cetuximab had significant activity. DL1 was established as the MTD.

Concomitant chemoradiotherapy improves survival in patients with non-resectable locally advanced esophageal cancer (LAEC) compared to radiotherapy alone as shown in the pivotal RTOG 85-01 trial (1) and in the meta-analysis by Wong and Malthaner (2). Hence, chemoradiotherapy with platinum and fluorouracil-derivatives is considered the standard therapy for medically fit patients. However, there is a need for new treatment approaches to improve survival, as outcomes remain poor for these patients. The EGFR-antibody cetuximab represents a potential new approach. The addition of cetuximab to radiotherapy substantially improved survival in squamous cell carcinoma of the head and neck – a malignancy that also originates from the upper digestive tract (3). Furthermore, a phase II trial showed that cetuximab could safely be administered with concurrent chemoradiotherapy in esophageal cancer (4). Data in advanced esophagogastric cancer indicate that oxaliplatin and oral capecitabine can replace cisplatin- and 5-fluorouracil-based combinations (5). The aim of this phase I trial was to evaluate the combination of radiotherapy, cetuximab, oxaliplatin, and tegafur/uracil in patients with non-resectable locally advanced carcinoma of the esophagus or of the gastro-esophageal junction (GEJ).

Patients and Methods

A phase I dose escalating trial of oxaliplatin and tegafur/uracil given concomitantly with radiotherapy and cetuximab was conducted in patients with non-resectable locally advanced carcinoma of the esophagus or GEJ. The patients were deemed non-resectable at a multi-disciplinary conference with oncologists, thoracic and upper abdominal surgeons. The primary end-points were the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) according to the NCI-CTC version 3.0. The secondary end-points were toxicity, response according to RECIST version 1.0, time-to-progression (TTP), and overall survival (OS).

The study protocol was approved by the Danish Medicines Agency (Eudract 2005-002658-23), the local ethical review board, and the Danish Data Protection Agency. The trial was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice.

Patients. Patients with histologically for confirmed non-resectable and locally advanced carcinoma of the esophagus or GEJ, Siewert type 1 and 2, were eligible. Operable patients who had declined surgery were also eligible treatment. Other inclusion criteria included measurable disease assessed by RECIST version 1.0, age between 18 and 75 years, life expectancy of more than three months, WHO performance status (PS) 0-2, and adequate bone marrow, hepatic, and renal functions. Major exclusion criteria included peripheral neuropathy greater than grade 1, other malignancies in the last five years except non-melanoma skin cancer, known allergy to components of the treatment, known dihydropyrimidine dehydrogenase deficiency, previous treatment with oxaliplatin, cetuximab, or radiotherapy prohibiting the delivery of 59.4 Gy.
Treatment plan. Escalating doses of oxaliplatin and tegafur/uracil were administered concurrently with radiotherapy in combination with cetuximab at a fixed dose (Figure 1). Chemotherapy at fixed doses was administrated before and after radiotherapy.

Radiotherapy. External beam radiotherapy was given as 59.4 Gy in 33 fractions of 1.8 Gy on days 22-66, five fractions per week. A three-field radiotherapy technique based on conformal CT planning was used in accordance with International Commission on Radiation Units and Measurements (ICRU) 50/62 recommendations. Prior to treatment a positron emission tomography (PET)-CT was performed with the patient in treatment position, and the PET-positive tumor was defined as gross tumor volume (GTV). A dose of 50.4 Gy (28 fractions) was delivered to the clinical target volume (CTV) i.e. the GTV including a margin of 35 mm distal and proximal and 10 mm laterally. A boost of 9 Gy (5 fractions) was given to the GTV only with a small planning target volume margin. Organs at risk were defined as the medulla, lungs, kidney, and liver. Constraints were maximally 46 Gy to the spinal cord, 20 Gy to 50 % of lung volume, and 17 Gy to 50 % of the kidneys.

Chemotherapy and cetuximab. One cycle of chemotherapy was administered before radiotherapy and two cycles of chemotherapy were administrated after radiotherapy. These cycles consisted of fixed doses of intravenous oxaliplatin (130 mg/m²) on days 1, 78 and 99, and oral tegafur/uracil (150 mg/m²) in combination with oral isovorin 15 mg twice daily, every twelve hours, on days 1-14, 78-91 and 99-112. An initial dose of intravenous cetuximab (400 mg/m²) was administrated before radiotherapy on day 15, followed by 250 mg/m² weekly for the duration of the radiotherapy treatment. Initially, intravenous clemastine at a dose of 2 mg was administrated 1 h prior to cetuximab infusion. After a serious allergic event, clemastine was supplemented with 50 mg intravenous ranitidine and 40 mg intravenous methylprednisolone in subsequent patients. During radiotherapy, oxaliplatin and tegafur/uracil were administered at escalating dose levels (DL) (Table I). Oxaliplatin was administrated every 2 weeks. Tegafur/uracil in combination with isovorin was administered during weekdays, twice daily, every 12 h during radiotherapy. Chemotherapy was administrated maximally 4 hours prior to radiotherapy. Standard antiemetics were used.

Definition of dose-limiting toxicities (DLTs). DLTs were defined as febrile neutropenia ≥ grade 3, or haematologic toxicity ≥ grade 4, or non-haematologic toxicity ≥ grade 3 except skin reaction, alopecia and adequately treated nausea and vomiting.

Dose escalation. Five different dose levels were planned. Cohorts of three patients were included at each dose level. If no DLT was observed, three patients were included on the next dose level. If one
Table III. Individual patients’ characteristics.

<table>
<thead>
<tr>
<th>Pt</th>
<th>DL</th>
<th>Age</th>
<th>Location</th>
<th>Type</th>
<th>TNM</th>
<th>Stage</th>
<th>Response</th>
<th>DLT</th>
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<td>T4N1</td>
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<td>NE</td>
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<td>Adenocarcinoma</td>
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<td>SCC</td>
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Squamous cell carcinoma (SCC), not evaluable (NE), complete response (CR), progressive disease (PD), stable disease (SD).

Results

A total of 11 patients were included from November 2006 to May 2008. Patients’ characteristics are summarized in Tables II and III. Ten patients were male. All patients had PS 0 or 1. The tumors were localised in the esophagus (n=8) or GEJ (n=3). The most predominant histology was squamous cell carcinoma (n=7), as compared to adenocarcinoma (n=4). Three patients were eligible for surgery. One declined surgery, one patient was declared non-resectable during exploratory laparotomy due to pleural involvement. A total of 9 patients completed the planned radiotherapy without interruptions. Seven patients were treated at DL 1, and four patients at DL 2. No grade 3 or grade 4 myelotoxicity was observed. Cetuximab-induced skin rash was observed as expected to maximum grade 2, with no worsening during radiotherapy. Two patients (one in DL 1 and one in DL 2) went off study on day 15 due to grade 3 and 4 allergic reactions to cetuximab. The first patient, on DL 1, developed a rash after the infusion of approximately 50 mg of cetuximab and subsequently suffered a cardiac arrest. The patient was successfully resuscitated and had a full recovery. The second patient, on DL 2, had a grade 3 allergic reaction to cetuximab. Neither of these two patients was evaluable for DLT and consequently substitute patients were enrolled at both DLs.

As no DLTs were reported in the first three patients treated at DL 1, the dose was escalated to DL 2. DLTs were observed in three out of three evaluable patients at DL 2. The first patient at DL 2 developed a tracheo-esophageal fistula grade 3 on day 99 and was taken off study. The third patient at DL 2 had a grade 4 tracheo-esophageal fistula which was observed 22 days after treatment was completed. The fourth patient in DL 2 had grade 3 neuropathy and treatment was interrupted on day 99. Therefore, three additional patients were enrolled at DL 1 with no DLT, and DL 1 was established as the MTD.

Statistical methods. Only patients that completed radiotherapy were included in the estimation of response, time-to-progression, and overall survival. Time-to-progression and overall survival were analysed using the Kaplan-Meier method. Analyses were conducted using the SPSS software version 18.
Response evaluation was performed according to RECIST 1.0 criteria on day 196. Four out of 9 patients had radiological complete response (CR) (Table IV). Notably, one of these had pathological CR (pCR) after surgery. One patient progressed during therapy, and two patients died during follow-up of cancer prior to response evaluation. One patient died before receiving the last fixed dose of oxaliplatin and tegafur/uracil.

Well aware of this small phase I trial and its low number of participants, the median overall survival (mOS) for reference was 13.2 months (95% CI 5.3 - >21). Median-time-to progression was 9.2 months (95% CI 0.4 -17.9). Two patients are still alive after 51 months of follow-up.

Discussion

The addition of cetuximab to concomitant chemoradiotherapy reported in the present trial showed significant activity with four out of 9 patients having radiological CR. The regimen also proved to be toxic with tracheo-esophageal fistula grade 3 and grade 4 developing in two out of three patients on DL2. In DL 1 there were no DLTs, and DL 1 was established as the MTD.

In two recent phase III trials acceptable toxicity and treatment-related mortality were reported when combining high dose radiotherapy (60-65 Gy) with standard chemotherapy (6, 7). Minsky et al. compared two different radiotherapy doses (50.4 Gy versus 64 Gy) combined with the same standard chemotherapy regimen (cisplatin and 5-FU), and recorded no benefit for local control or overall survival with the higher radiotherapy dose (8). Based on these data, a dose of 50.4 Gy is still considered the standard of care according to the 2011 National Comprehensive Cancer Network (NCCN) guidelines.

The addition of cetuximab to chemoradiotherapy has been explored in several phase I/II trials, and has been mainly regarded as safe (4, 9-11). A recent phase II trial confirmed that cetuximab can be safely administered with concomitant chemotherapy (carboplatin and paclitaxel) and 50.4 Gy radiotherapy without an increase in esophagitis or cetuximab-induced skin rash during radiotherapy (4). Forty out of 57 patients (70%) had a complete clinical response; esophagitis grade 3 and 4 was seen in 12% and 3%, respectively. In the phase II EraFox study, 80 patients received chemotherapy with FOLFOX and cetuximab and 50.4 Gy radiotherapy (10). An overall response rate of 77.2% was reached and the regimen proved feasible with an acceptable frequency of grade 3/4 esophagitis. A recent phase II trial investigating induction therapy with oxaliplatin, 5-FU and cetuximab, followed by radiotherapy 50.4 Gy and cetuximab reported a pCR rate of 27%, mOS 17.3 months, and 3-year OS of 42% (11). The regimen also proved to be safe with mainly grade 1/2 esophagitis. In contrast, another phase II trial of neoadjuvant chemoradiotherapy using a lower dose of radiotherapy (45 Gy in 28 fractions) with oxaliplatin, 5-FU and cetuximab, followed by postoperative docetaxel plus cetuximab was stopped after the recruitment of 22 patients due to unacceptable toxicity, although showing promising activity with a pCR rate of 32% (12). Seven died on study, including 4 postoperative deaths caused by acute respiratory distress syndrome (ARDS). Additionally, in a recently reported phase II trial concurrent cetuximab, cisplatin, irinotecan and radiotherapy with 50.4 Gy was poorly tolerated with treatment-related mortality approaching 10% (13). Thirty-eight % of the patients exhibited grade 4/5 toxicity with treatment-related mortality in two patients (sudden death, gastrointestinal necrosis). Efficacy was modest with response rate of 17.6%, including only one complete response (5.9%), median OS was 11.2 months, two-year survival 33%. An ongoing multicentre, phase II/III trial (SCOPE-1) will further evaluate chemoradiotherapy with or without cetuximab (14).

Oxaliplatin and 5-FU, concomitant with radiotherapy at a dose of 50 Gy, have shown promising results and acceptable toxicity in phase I and II trials (15). When increasing the dose of radiotherapy, slightly higher toxicity was described in a recent phase I/II trial where an oxaliplatin-containing regimen was given concomitantly with radiotherapy up to a total dose of 64.8 Gy (16). The regimen was found to be effective with a pCR rate of 49% and mOS of 24 months, but at the expense of increased toxicity, with 20% of patients experiencing esophagitis grade 3/4 and 10% grade 4 pulmonary complications (16). In a randomised phase II trial including 97 patients, oxaliplatin and 5-FU (FOLFOX-4) were superior to cisplatin and 5-FU given concomitantly with 50 Gy radiotherapy with mOS of 22.7 months in the FOLOX-4 arm, compared to 15.4 months in the control arm (17).

Conclusion

In our trial, the combination of a high radiotherapy dose of 59.4 Gy concomitant with oxaliplatin-based chemotherapy, and with the addition of cetuximab is likely to be responsible for the excess toxicity found. The reported chemoradiotherapy regimen is not attractive for further evaluation in a phase II design due to the observed toxicity.
In DL 1 (tegafur/uracil 150 mg/m², Oxaliplatin 30 mg/m²²) there were no DLTs, and DL 1 was established as the MTD.

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References


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