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von Döbeln, Gabriella Alexandersson; Wagenius, Gunnar; Holtved, Eva; Jacobsen, Anne Birgitte; Nilsson, Magnus; Yu, Jingru; Baeksgaard, Lene

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Definitive chemoradiotherapy plus cetuximab for cancer in the oesophagus or gastro-oesophageal junction

Gabriella Alexandersson von Döbeln, Gunnar Wagenius, Eva Holtved, Anne-Birgitte Jacobsen, Magnus Nilsson, Jingru Yue, Lene Baeksgaard

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ABSTRACT

Background: Chemoradiotherapy is standard treatment for localized oesophageal cancer unsuitable for surgery. We aimed to evaluate the efficacy of cetuximab in combination with chemoradiotherapy.

Methods: This non-randomised multicentre phase II trial recruited patients aged 18-75 with WHO performance status 0-2 having squamous cell carcinoma or adenocarcinoma in the oesophagus or gastro-oesophageal junction, T2-4, N0-3, M0 not suitable for surgery. Chemotherapy was three 21-day cycles of fluorouracil 750 mg/m² D1-5 and oxaliplatin D1 (cycle 1:130 mg/m², cycle 2-3:85 mg/m²). Radiotherapy was 50 Gy in 2 Gy/fraction, 5 days a week, concurrent with cycle 2 and 3 and weekly cetuximab. The primary objective was loco-regional control at one year.

Results: 52 patients were included. 51 were eligible for toxicity and survival analysis and 46 for recurrence analysis. Full radiotherapy dose was delivered to 80%, 75% received all three cycles of chemotherapy and 75% received four or more doses of cetuximab. The most common related grade III-IV adverse events were gastrointestinal (16), hypersensitivity (6) and infection (5). There were two drug-related deaths. Within six months from the end of treatment, six patients died from complications from fistulas. The loco-regional control rate at one year was 47.3% (95% CI 30.9%-62.1%). Overall survival at three years was 29.1% (95% CI 17.4-41.9%).

Conclusions: Oxaliplatin and fluorouracil given concurrent with radiotherapy and cetuximab had an acceptable safety profile and showed a clinical response in patients with locoregionally advanced oesophageal cancer unsuitable for surgery. However, the primary end-point was not met, and the addition of cetuximab to definitive chemoradiotherapy cannot be recommended.

Introduction

Cisplatin and fluorouracil in combination with radiotherapy have since long been the standard treatment for localised inoperable or non-resectable oesophageal cancer [1]. In recent years, oxaliplatin with a more favourable toxicity profile than cisplatin, has emerged as an optional platinum analogue as it seems to be as effective as cisplatin [2,3]. Still, the survival is poor [4] and better treatment strategies are needed.

High expression of the transmembrane protein epidermal growth factor receptor (EGFR) has been shown to be a negative prognostic factor in patients with adenocarcinoma or squamous cell carcinoma in the oesophagus [5,6]. When activated, EGFR causes the activation of intracellular pro-oncogenic pathways. This is the rationale behind targeting the EGFR pathway with drugs such as cetuximab, which bind to the extracellular domain of the EGFR and block intracellular signalling.

In clinical trials, the addition of cetuximab to radiotherapy or chemotherapy has improved survival in patients with head and neck cancer [7,8] and advanced colorectal cancer [9]. At the time this trial was initiated, early clinical data suggested a beneficial effect from the addition of cetuximab to chemoradiotherapy also in patients with oesophageal cancer [10].

Taken together, these preclinical and clinical data provided the
rationale to evaluate the addition of cetuximab to oxaliplatin, and fluorouracil given concomitantly with radiotherapy in patients with localised cancer of the oesophagus or cardia. Within the Scandinavian Esophageal and Gastric cancer group, we conducted a prospective, non-randomised, multicentre study: LERFOX-C. The primary endpoint was loco-regional control at one year. Secondary endpoints were toxicity, patterns of relapse, progression-free survival, and overall survival.

Patients and Methods

Eligibility criteria

Patients had to be 18-75 years old, have a WHO performance status of 0-2, have an untreated histologically proven adenocarcinoma or squamous cell carcinoma of the oesophagus or oesophagogastric junction (type I and II according to Siewert’s classification [1]) with the clinical stages T2-T4, N0-N3, M0 according to the American Joint Committee on Cancer tumour-nodes-metastasis staging system 7th edition. Patients had non-resectable tumours or were considered non-operable for medical reasons. A computed tomography (CT) of the thorax and abdomen was required. An endoscopic ultrasound of the oesophagus was recommended and a positron emission tomography (PET) with fluorodeoxy glucose (FDG) was optional. The study was approved by Research Ethics Committees in Sweden, Denmark and Norway. Registration number in ClinicalTrials.gov: NCT02636088. All participating patients provided written informed consent.

Treatment

Chemotherapy

Patients were scheduled for three 3-weekly cycles of fluorouracil 750 mg/m²/24 hours, days 1-5 and oxaliplatin day 1. Oxaliplatin was given with 130 mg/m² in the first cycle. In the second and third cycles it was administered concomitantly with radiotherapy and the dose was reduced to 85 mg/m².

Cetuximab

A loading dose of 400 mg/m² was given one week before the start of radiotherapy, and thereafter 250 mg/m² was given weekly during the course of radiotherapy. Cetuximab was given at least one hour before the infusion of oxaliplatin and radiotherapy.

Radiotherapy

Concomitant with chemotherapy, 50 Gy was given (2 Gy once daily in 25 fractions, 5 days a week) with a photon beam linear accelerator. A three-dimensional dose planning system was used. The boost clinical target volume (CTV30Gy) was to embrace in the lateral, anterior and posterior directions the gross tumour volume (GTV) with a margin of 1 cm, although respecting anatomical barriers such as pleura, pericardium and bone. Cranially and caudally, a margin of 20 mm to GTV was recommended. For tumours located mainly above the carina, the caudal border of the CTV46 Gy was to include another 3 cm caudally of CTV50 Gy and the supraclavicular nodes defined the upper border. For tumours located mainly below the carina, the cranial border of the CTV46 Gy was 3 cm cranial of the CTV50 Gy and the lower border was defined by the coeliac lymph nodes. The planning target volume was according to local routines. Maximum tolerated dose to the spinal canal was 45 Gy, dose to the lungs was not to exceed 20 Gy to 30% of the volume, dose to the heart was not to exceed 40 Gy to 50% of the volume and dose to the kidneys was not to exceed 17 Gy to 50% of the volume.

Statistical analysis

The treatment was to be considered promising if the loco-regional control rate at one year was above 50%, but not of further interest if the loco-regional control rate at one year was 50% or less. With the use of a two-sided test with 0.80 statistical power and a significance level of 0.05, the trial needed 85 eligible patients. With the acquired 51 patients, the power of the trial was 0.58. The time-to-event was estimated with the Kaplan-Meier method. Loco-regional control rate was calculated from the time of registration until loco-regional progression assessed with a CT with or without the addition of PET and endoscopy. Fistulas were categorised as loco-regional tumour progression, unless there was benign pathology and radiographic response. If no radiotherapy was given, the time for loco-regional progression was set at the date when the decision was made not to give radiotherapy. Patients were censored at the last follow-up visit, at 36 months after registration or at the date of death if there were no signs of loco-regional failure. Progression-free survival was defined as the time from registration until progression or death from any cause. If oesophageal resection was performed, the date of progression was set at the date of surgery if there was cancer in the resected specimen. Living patients without signs of tumour recurrence were censored at the last follow-up visit or 36 months after registration, whichever came first. Overall survival was defined as the time from registration until death. Living patients were censored at the last follow-up visit or 36 months after registration.

Follow-up visits including a CT-scan were planned four weeks after the end of treatment, and then every sixth month until 36 months after registration. An optional FDG-PET was planned 12 months after registration.

Results

Patient characteristics

Inclusion was prematurely stopped after results from two randomised clinical trials, RTOG 0436 and SCOPE-1, showing no benefit from the addition of cetuximab to definitive chemoradiotherapy [12-14]. Fifty-two patients from 11 participating institutions in Sweden, Denmark and Norway were registered between March 2011 and September 2014. Four institutions included only one patient. The flow chart of the trial is presented in Fig 1. Demographic and clinical characteristics are detailed in Table 1.

Treatment delivery

A total of 41 patients (80%) received full radiotherapy treatment (one received 54 Gy to compensate for a short break in the treatment and one received 64 Gy because of a misunderstanding), 38 (75%) received all three cycles of chemotherapy and 38 (75%) received four or more of the planned six doses of cetuximab. For those who received 50 Gy, the median overall treatment time for radiotherapy was 35 days (range, 33-40 days). Among patients selected for non-surgical treatment due to medical unfitness 9 (69%) received full radiotherapy, three cycles of chemotherapy and at least four doses of cetuximab. The corresponding number of those with non-resectable tumours (due to cervical location or local extent of tumour) was 24 (63%).

Adverse events

Treatment-related adverse events were graded according to the US National Cancer Institute's Common Terminology Criteria for Adverse
Events (CTCAE) version 4.03. Relation to study treatment was possible, probable or certain. Twenty-six patients experienced at least one related adverse event grade III and IV during treatment. Reported events were gastrointestinal (16), hypersensitivity (6), infection (5) skin rash (4), recorded only once were hyponatremia, hypopotassemia, anaemia, neutropenia, pain, fatigue, tinnitus, septicemia, elevation of cardiac troponin T, hypotension, syncope, dyspnoea and pneumonitis.

Three patients died before treatment started or in the early phase of treatment: one from tumour bleeding before treatment started; one from oesophageal necrosis after the first course of chemotherapy before cetuximab was given, probably related to toxicity from fluorouracil and one from suffocation due to tumour progression after two courses of chemotherapy, four courses of cetuximab and 18 Gy.

One patient died within four weeks from the end of treatment due to interstitial lung disease probably related to oxaliplatin and/or cetuximab.

One patient was found to have distant metastases after only one course of chemotherapy.

Six patients died within six months from the end of treatment due to complications from fistulas between the oesophagus and airways (three patients) or aorta (three patients). All these patients had squamous cell carcinoma. None of them had known fistulas before the initiation of treatment. Patients who developed fistulas had been selected for definitive chemoradiotherapy rather than surgery due to local extent of tumour (five patients) and medical unfitness (one patient). Two had microscopic findings of tumour in the fistula at the post-mortem. One had no pathological or radiographic signs of tumour. Three had no clinical signs of tumour progression, although endoscopic evaluations and post-mortems were not executed, and a CT-scan had been done in only one patient. All six had received four or more infusions of cetuximab, five had received 50 Gy and one had received 38 Gy. There was no significant association between pre-treatment dysphagia score and T-stage and fistula formation.

Response to treatment

Of the 42 patients who received at least one chemotherapy cycle and 20 Gy, 26 patients (62%) responded to chemoradiotherapy, partially (36%) or completely (26%). Ten (24%) had stable disease, four (10%) had progressive disease and two were not assessable.

There was no significant difference in the response rate between patients with adenocarcinoma and squamous cell carcinoma.

Loco-regional control

The probability of loco-regional control at one year was 47.3% (95% CI 30.9% - 62.1%) as displayed in Fig. 2. Twenty-three patients died during the first year after registration of whom 9 had no evidence of loco-regional relapse and were therefore censored. In multivariate analysis, patients selected for non-surgical treatment because of cervical location of the tumour had a better loco-regional control rate than those selected for chemoradiotherapy due to local extent of the tumour. They also seem to have a better loco-regional control rate than those selected for non-surgical treatment due to medical unfitness. Details in Table 2.
The present trial evaluated the addition of cetuximab to oxaliplatin and fluorouracil given concurrent with radiotherapy, to patients with localised oesophageal cancer selected for non-surgical treatment. The estimated loco-regional control rate at one year was 47% and three-year overall survival was 29%. Previous studies on definitive chemoradiotherapy show three-year survival rates ranging from 24% to 45% [4,15-17]. Direct comparisons between the trials are hampered by the fact that there are substantial differences in patient- and tumour characteristics between the trial cohorts.

Loco-regional failure is high in patients with oesophageal cancer treated with curatively intended chemoradiotherapy, and results from the current trial are consistent with previously reported data although the heterogeneity in baseline characteristics between trials makes direct comparisons difficult [16,18]. Nevertheless, it seems as though patients selected for non-surgical treatment due to cervical location of the tumour had a better prognosis than those with patient-related factors or local extent of the tumour making them unsuitable for surgical resection. Patients with cancer located in the cervical part of the oesophagus are preferably treated with non-surgical methods as it increases the chance of larynx preservation without decreasing the chance of survival [19]. As their general condition is not the main reason to abstain from surgery, they are more likely to tolerate chemoradiotherapy than patients selected for non-surgical treatment due to medical unfitness, and this could explain the differences in tumour control. Also, it has previously been shown that patients selected for non-surgical treatment because of extensive non-resectable tumour are less likely to have a long-term benefit from treatment than those not operated on due to patient-related factors [15]. Consequently, they are less likely to benefit from chemoradiotherapy compared to those selected for non-surgical treatment due to cervical location of the tumour, which is confirmed in our trial.

Recently two randomised clinical trials, SCOPE-1 [12,13] and RTOG...
0436 [14], have failed to show any survival advantage when adding cetuximab to definitive chemoradiotherapy in the treatment of oesophageal cancer. However, in the SAKK 75/08 trial where cetuximab was added to neoadjuvant chemoradiotherapy, the addition of cetuximab significantly improved loco-regional control even though this was not translated into a statistically significant increase in overall survival [20]. The results could indicate that there is a subset of patients with oesophageal cancer who might benefit from the addition of cetuximab to chemoradiotherapy. Molecular features of the tumour is likely to predict response, although the search for such markers has this far been disappointing [21]. Moreover, it is reasonable to believe that it matters what drugs are combined with cetuximab. When cetuximab was added to capecitabine, cisplatin and radiotherapy in SCOPE-1, treatment intensity including radiotherapy dose was decreased. In contrast, in RTOG 0436 and SAKK 75/08, where cetuximab was added to cisplatin, paclitaxel and radiotherapy, a decrease in treatment intensity was not reported. Two meta-analyses in upper GI cancer [22] and colorectal cancer [23] have reached the conclusion that anti-EGFR treatment combined with capecitabine or bolus-fluorouracil results in worse survival than if used with infusional fluorouracil. In contrast to SCOPE-1, we used infusional fluorouracil rather than capecitabine in addition to platinum and radiotherapy and despite the predominance of T4 tumours and as many as 14% of patients having a performance status 2, the treatment intensity in the present trial reached levels well comparable to other trials, which indicates good tolerability of given treatment. Also, the toxicity profile in our trial is similar to previously reported data from definitive chemoradiotherapy aside from higher rates of hypersensitivity reactions and skin rash. Altogether, we may conclude that toxicity from the oxaliplatin-fluorouracil-cetuximab-radiotherapy regimen is not negligible, but acceptable in these high-risk patients.

The vulnerability of this group of patients is further illustrated by the fact that within six months from the end of treatment, six patients (12%) died from complications from fistulas between the oesophagus and adjacent organs. Fistulas may develop after chemoradiotherapy, and when the tumour is susceptible for treatment and becomes necrotic. But, fistulas can also be the natural progression of the disease and it is often difficult to distinguish between the two. Tsushima et al found symptoms from pre-treatment stenosis to be a risk factor for the development of fistulas [24], whereas Taniguchi et al found in a retrospective analysis low serum cholesterol to be associated with oesophagogastric fistulas [25]. We did not find T4-disease or pre-treatment stenosis measured as dysphagia score to be risk factors for fistula formation, which could be attributed to the small number of patients in our trial. Previously reported incidence of fistulas after definitive chemoradiotherapy varies as there are substantial differences in patient- and tumour characteristics between the trial cohorts. Crosby et al. found an incidence of 4% [15], whereas Tsushima et al. reported an incidence of almost 18% in a cohort of patients with a majority of patients having a primary tumour invading nearby organs [24]. From the two randomised trials adding cetuximab to definitive chemoradiotherapy fistulas were reported in one [14]. They found a lower
compared to other trials that cetuximab would increase the risk of addition of cetuximab did not seem to increase the risk of much smaller number of patients with T4 disease in that trial. The conclusion that oxaliplatin and chemotherapy and radiotherapy.

we conclude that oxaliplatin and fluorouracil given concurrent with radiotherapy and cetuximab is tolerable and showed a clinical response even in high-risk patients with loco-regionally advanced oesophageal cancer not suitable for surgery. However, the primary endpoint was not met and the addition of cetuximab to definitive chemoradiotherapy cannot be recommended.

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Declaration of Competing Interest

The authors declare no conflicts of interest.

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