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Phase II study of biweekly cetuximab in combination with irinotecan as second-line treatment in patients with platinum-resistant gastro-oesophageal cancer

K.R. Schønnemann [a,c,*], M. Yilmaz [b], J.K. Bjerregaard [a,c], K.M. Nielsen [b], P. Pfeiffer [a,c]

[a] Department of Oncology, Odense University Hospital, Odense, Denmark
[b] Department of Oncology, Aalborg Hospital, Aalborg, Denmark
[c] Institute of Clinical Research, University of Southern Denmark, Odense, Denmark

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Abstract *Background:* The purpose of this phase II trial was to evaluate the efficacy and safety of cetuximab and irinotecan as second-line treatment in patients with gastro-oesophageal adenocarcinoma.
Patients and methods: Patients with failure to first-line platinum-based chemotherapy received cetuximab 500 mg/m^2 and irinotecan 180 mg/m^2 every second week until disease progression. Toxicity was evaluated according to The Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v. 3.0. Antitumour activity was assessed according to Response Evaluation Criteria in Solid Tumours (RECIST) v. 1.0.
Results: Sixty-three patients were enrolled, median age was 60 years, median performance status was 1 (0–1), 35 patients had two or more organs involved. The median number of courses was 5 (range 1–25). Response rate was 11% (6 partial response (PR)) and 37% had stable disease. Median progression free survival was 2.8 months and overall survival (OS) was 6.1 months. Grade 3–4 toxicity included: diarrhoea (6%), fatigue (5%), vomiting (5%) and neutropenia (16%). Two patients developed febrile neutropenia. Forty-six patients (73%) had developed grade 1–2 skin rash. Patients developing skin rash had a prolonged survival with an OS at 7.1 months.
Conclusions: The combination of cetuximab and irinotecan is active as second-line therapy in patients with gastro-oesophageal cancer. Cetuximab induced skin rash was associated with prolonged survival.

1. Introduction

Gastro-oesophageal cancer (GEC) is the fourth most common cancer and the second most common cause of

* *Corresponding author at:* Department of Oncology, Odense University Hospital, Sdr. Boulevard 29, 5000 Odense C, Denmark. Tel.: +45 65 41 38 34, mobile: +45 26 20 39 60; fax: +45 66 13 54 77.
E-mail address: k.schoennemann@ouh.regionsyddanmark.dk (K.R. Schønnemann).

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cancer related death worldwide.[1,2] In patients with recurrent, advanced or metastatic GEC randomised trials have provided evidence that systemic chemotherapy palliates symptoms and significantly improves survival (OS) and quality of life.[3,4] Historically, patients with adenocarcinoma of the GEC have been treated as a single entity in regard to the efficacy and toxicity of chemotherapy.[5] At present there are several standards of first-line chemotherapy in GEC. Two cornerstones are 5-fluorouracil (5-FU) and platinum derivatives that are widely accepted as the 'drugs of choice' in the first-line setting, obtaining response rates (RR) of 25–40%. Although many patients primarily respond to first-line treatment, the median OS is still less than one year after diagnosis.[6–9] Beyond progression on first-line therapy patients have a dismal prognosis. Some patients are however still in a good performance status (PS), leading to interest in an effective and tolerable second-line treatment. Irinotecan has proven activity in GEC patients both as a single agent and in combination with other modalities. In the second-line setting irinotecan as a single agent has achieved RR of 16–20% in advanced GEC patients.[10,11] Presently, two randomised phase III studies have demonstrated a prolonged OS in favour of irinotecan compared to best supportive care (BSC).[12,13] Based on these studies irinotecan can be considered as a relevant treatment option in the second-line setting.

Recently, an increased understanding of the molecular basis of cancer has led to the development of specific *molecular-targeted* agents. The epidermal growth factor receptor (EGFR) has been found to be over-expressed in 10–63% of gastric cancers.[14] EGFR over-expression is associated with tumour progression and poor prognosis in GEC patients, providing the rational for targeting this receptor in GEC.[15]

The anti-EGFR monoclonal antibody, cetuximab is usually administered weekly, but pharmacokinetic studies in patients with metastatic colorectal cancer (mCRC) have demonstrated no major differences between cetuximab 250 mg/m^2 weekly versus 500 mg/m^2 every second week.[16–18] Furthermore a simplified administration with only two hospital visits per month is more desirable for patients with severe disease. In the first-line setting the combination of chemotherapy and cetuximab has demonstrated promising results in GEC patients leading to interest in second-line use. Two phase II trials have investigated salvage therapy with cetuximab as a single agent. Both trials concluded that cetuximab seemed to have a minimal activity in pre-treated GEC patients.[19,20] Based on results from the two above mentioned trials cetuximab as a single agent is not a relevant treatment option as second-line therapy in GEC patients. In this phase II trial we therefore investigated the biweekly combination of cetuximab and irinotecan in order to evaluate efficacy and toxicity.

2. Materials and methods

2.1. Patient selection

The study included patients with histological confirmed, evaluable or non-evaluable, non-resectable or metastatic adenocarcinoma of the lower oesophagus, oesophageal-junction or stomach. All patients had received prior platinum-based chemotherapy and demonstrated progressive disease after or during previous treatment. The eligibility requirements included a PS of 0–1; age >18 years and a life expectancy of at least 12 weeks. Preclinical laboratory parameters included an adequate bone marrow function (neutrophils $>1.5 \times 10^9$/L, platelets $>100 \times 10^9$/L); adequate hepatic function (serum bilirubin $<1.5 \times$ upper normal limit (UNL), in case of liver metastases, there were no upper limit for transaminases). Patients were ineligible if they had severe medical illnesses or another active malignancy. Females were not included if they were pregnant or lactating. The study was approved by the local ethics committee and the Danish Health Authority and written informed consent was obtained from all patients before study entry, according to the Helsinki declaration.

2.2. Treatment

Irinotecan 180 mg/m^2 and cetuximab 500 mg/m^2 was administered on day 1 every second week.[21] The first course of cetuximab was infused in 120 min followed 1 h later by irinotecan. Subsequent courses of cetuximab were infused in 60 min, immediately followed by irinotecan as a 30 min infusion. Patients received premedication with antihistamine (e.g. 2 mg clemastine i.v.) to minimise the risk of infusion-related reactions associated with cetuximab. Before cetuximab infusion patients also received antiemetic with oral prednisolone 100 mg and oral ondansetrone 8 mg $\times$ 2. Treatment continued until disease progression, patient refusal or unacceptable toxicity.

2.3. Evaluation of toxicity and dose adjustment

Toxicity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (NCI-CTCAE). In case of NCI-CTCAE grade 3 or 4, the dose of irinotecan was reduced by 25% in the subsequent treatment cycles. If patients developed skin rash (acneiform) grade 3 the dose of cetuximab was postponed until recovery to grade $\leqslant 2$. In case of recurrent episodes of skin rash grade 3, the dose of cetuximab was reduced 20% in the subsequent treatment cycles. Patients developing skin rash, any grade, were offered tetracycline in order to reduce symptoms and risk of infection.