ORIGINAL ARTICLE

Biweekly cetuximab and irinotecan as second-line therapy in patients with gastro-esophageal cancer previously treated with platinum

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Abstract

Background Until recently there has been no proven second-line therapy for patients with advanced gastro-esophageal cancer (GEC). Since 2004, Denmark has had a national health program where non-proven therapy can be offered to patients with advanced cancer, after approval by an expert panel appointed by the National Board of Health. This program has accelerated the introduction and implementation of new therapies in Denmark. Inspired by therapy in metastatic colorectal cancer, a combination of cetuximab and irinotecan (Cetiri) was chosen for second-line therapy in GEC patients. We report our experience with Cetiri as second-line therapy in patients with GEC.

Methods All patients had histologically confirmed GEC and all patients had progressive disease during or after first-line platinum-containing chemotherapy. The patients received cetuximab 500 mg/m^2 on day 1 and irinotecan 180 mg/m^2 on day 1 every 2nd week until progression or unacceptable toxicity. Toxicity was prospectively evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0.

Results From December 2007 to February 2009, 50 consecutive patients received Cetiri as second-line therapy. Median performance status (PS) was 1. The median number of courses was seven. Seven patients (14%) had a partial response. Median progression-free survival (PFS) was 3.3 months and overall survival (OS) was 5.5 months; two patients are still alive without progressive disease. Major toxicities were: diarrhea (8%), fatigue (10%), neutropenia (16%), and febrile neutropenia (2%).

Conclusion Cetiri every two weeks is a convenient and well-tolerated second-line regimen in GEC patients. A promising effect was seen in patients with PS 0-1 and in patients who developed a rash.

Keywords Stomach neoplasm · Cetuximab · Irinotecan · KRAS protein · Second-line therapy

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Introduction

Despite a declining incidence of gastro-esophageal cancer (GEC) in developed countries it is still the second most common cause of cancer-related deaths worldwide [1, 2]. For patients with non-resectable disease or recurrent disease, palliative chemotherapy prolongs survival and improves quality of life [3, 4]. Adenocarcinoma of the esophagus, esophagogastric junction, and the stomach is often regarded as a single entity in regard to the efficacy and toxicity of chemotherapy [5]. At present, there are several standards for chemotherapy regimens for first-line therapy, but most often platinum-based therapies are used, with response rates (RRs) between 25 and 45%, and a prolongation of median

overall survival (OS) to 7–10 months [6, 7]. Patients who progress on first-line therapy have a dismal prognosis, with an expected median survival of a few months. However, many patients still have an excellent performance status (PS), leading to interest in second-line therapy. Until recently, there was no established second-line therapy in GEC patients, but a new small randomized study demonstrated a prolonged OS in favor of irinotecan compared to best supportive care [8]. Irinotecan is a topoisomerase-1 inhibitor with proven activity in GEC patients, both as a single agent and in combination with other modalities, including 5-fluorouracil (FU) and cisplatin [9–11]. Epidermal growth factor receptor (EGFR) is over-expressed in 40–60% of GEC patients. Cetuximab is a monoclonal antibody against the EGFR and has shown activity in metastatic colorectal cancer (mCRC) where response to therapy is strongly correlated with the mutational status of KRAS. The combination of cetuximab and irinotecan is active in irinotecan-refractory mCRC patients, with a favorable toxicity profile [12]. Usually cetuximab is administered on a weekly schedule, but pharmacokinetic studies in patients with mCRC have demonstrated no major differences between cetuximab 250 mg/m^2 weekly versus cetuximab 500 mg/m^2 every second week [13–15]. Administration of a simplified regimen that does not compromise efficacy is desirable for both patients and hospital personnel.

Since 2004, Denmark has had a national health program where non-proven therapy can be offered to patients with advanced cancer, after approval by a Second Opinion Panel appointed by the National Board of Health. This program has had a major impact on the management of cancer patients in Denmark and has accelerated the introduction and implementation of new drugs [16]. Inspired by the high incidence of EGFR over-expression in GEC patients and the promising results seen in patients with mCRC, cetuximab and irinotecan (Cetiri) was administered every second week [17] as experimental second-line therapy in GEC patients whose disease had progressed during or after platinum-based chemotherapy.

Patients, materials, and methods

In this compassionate-use series, 50 consecutive patients were registered and treated in a single experimental cancer unit. Treatment was, in all patients, recommended by the Danish Second Opinion Panel. Before the start of treatment, patients were evaluated and informed about the experimental therapy with biweekly Cetiri. All patients selected for treatment had histologically verified, evaluable or non-evaluable, non-resectable adenocarcinoma of the esophagus, esophageal junction, or stomach. All patients had received prior platinum-based chemotherapy and had

demonstrated progressive disease during or after previous treatment. Standard adequate laboratory tests, including hematology and renal and hepatic function tests, were required prior to treatment. Response was evaluated by the investigators according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.0. Patients with non-measurable disease at the start of treatment and without signs of progression after 4 cycles of Cetiri (2 months) were considered to have stable disease (SD).

Treatment

It was planned that patients were to receive a combination of irinotecan 180 mg/m^2 and cetuximab as a 500 mg/m^2 infusion on day 1 (Cetiri) every second week [17]. The first course of cetuximab was infused in 120 min (min) followed 1 h later by irinotecan. Subsequent courses of cetuximab were infused in only 60 min, immediately followed by irinotecan given in 30 min, resulting in an overall treatment time of 90 min. Therapy was repeated every second week until unacceptable toxicity or disease progression. Patients received premedication with oral prednisolone 100 mg and an antihistamine, e.g., 2 mg clemastine i.v., to minimize the risk of infusion-related reactions associated with cetuximab, as well as antiemetics and oral ondansetron 8 mg × 2 before the irinotecan infusion. In order to prevent irinotecan-associated acute cholinergic syndrome, 0.25 mg atropine was given s.c. or as a slow i.v. infusion. Two patients were offered irinotecan (250 mg/m^2) and panitumumab (9 mg/kg) every three weeks due to their having an exceptionally long transportation time to the hospital.

DNA extraction and KRAS mutation analysis

KRAS mutation analysis was performed on tissue samples from the first 28 patients treated with Cetiri. The tumor samples were obtained from the primary gastric tumors (n = 23) or metastatic tissue (n = 5). DNA was extracted from formalin-fixed paraffin-embedded (FFPE) tissue sections, using a MagNA Pure LC DNA Isolation Kit (Tissue) (Roche). Samples were included for the analysis after histological verification of the presence of more than 70% tumor cells in each tumor sample. KRAS mutation analysis was performed as a real-time polymerase chain reaction (PCR), using a TheraScreen® KRAS mutation kit (DxS, Manchester, England) according to the manufacturer's protocol. The seven most common KRAS point mutations in codons 12 and 13 were detected in the analysis. Each sample was analyzed in duplicate.

Evaluation of toxicity and dose adjustment

Adverse events were prospectively evaluated and recorded before each course according to the National Cancer

Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. In patients with CTCAE grade 3 or 4 adverse events, the dose of irinotecan was reduced by 25% in the subsequent treatment cycles. If patients developed grade 3 skin toxicity, the dose of cetuximab was postponed until recovery to grade ≤2; in those with recurrent episodes of grade 3 skin toxicity, the dose of cetuximab was reduced by 20% in the subsequent treatment cycles.

Statistical considerations

Progression-free survival (PFS) was calculated as the period from the first infusion of Cetiri to the first observation of radiological or clinical disease progression or death of any cause. OS was calculated as the period from the first infusion of Cetiri until death of any cause. Data were updated in December 2010. Survival analyses were performed using the Kaplan–Meier method. In order to establish prognostic factors for OS, a multivariate model was fitted, using Cox regression, to known and collected clinically relevant prognostic factors. Because of the limited numbers of patients only six parameters were included in the multivariate Cox regression model. Performance status (PS) was divided into three groups; PS = 0, versus PS = 1 versus PS = 2. Time to progression (TTP) under first-line chemotherapy was included as a continuous variable and was defined as the period from the start of first-line chemotherapy to the first date of Cetiri. The number of metastatic sites was divided into two groups; 1–2 versus ≥3. Skin toxicity was included in the model as any rash versus no rash, and blood samples were dichotomized at the upper normal limit.

Results

Patient characteristics

From December 2007 to February 2009, 50 consecutive patients were treated at our experimental unit. Patient characteristics are listed in Table 1. Median age was 61 years (range 29–76). The majority of patients (40) were men (80%). The location of the primary tumor was the esophagus in two patients, gastro-esophageal junction in 32, and stomach in 16. Forty-five patients had metastatic disease. At baseline 17 patients had PS 0 (34%), 27 patients had PS 1 (54%), and six patients had PS 2 (12%). All patients had received prior platinum-based combination chemotherapy.

Toxicity

All patients were evaluable for toxicity. In general, the treatment was well tolerated; the worst CTCAE toxicities

Table 1 Baseline characteristics

Number of patients	50
Age, years (median) range	61 (range 29–76)
Male/Female	40/10
PS	
Median	1
0	17 (34%)
1	27 (54%)
2	6 (12%)
Primary tumor site, n (%)	
Esophagus	2 (4)
Gastro-esophageal junction	32 (64)
Stomach	16 (32)
Stage, n (%)	
Locally advanced	5 (10)
Metastatic	45 (90)
Number of metastatic sites, n (%)	
1–2	25 (50)
≥3	25 (50)
Median TTP under first-line CT (range)	4.5 months (1.5–13) months

PS performance status, *TTP* time to progression, *CT* chemotherapy

are listed in Table 2) Non-hematological toxicities were mainly grade 1–2; fatigue (72%), diarrhea (48%), nausea (70%), vomiting (30%), and skin toxicity (65%). Only four patients (8%) had diarrhea grade 3. Hematological toxicities of grade 3–4 were neutropenia (16%) and febrile neutropenia (2%). Two patients died before receiving the second course of therapy, one patient due to intestinal volvulus and one patient due to pulmonary embolism.

KRAS mutation analysis

Mutation analysis of *KRAS* codons 12 and 13 was retrospectively planned in all patients. However, in eight of the first 28 patients it was not possible to conduct the *KRAS* mutation analysis because of very sparse tumor tissue. Among the 20 patients analyzed, only two tumors (10%) had a *KRAS* mutation, one in p.Gly12Asp and one in p.Gly12Cys. Eighteen tumors were *KRAS* wild-type. The two patients with the *KRAS* mutation received 1 and 28 courses of Cetiri, respectively. The patient receiving only one cycle was hospitalized shortly after the first treatment with intestinal volvulus and died following this. The other patient, who received 28 courses, obtained a partial response (PR) during treatment and had an R0 resection. Because of the low incidence of *KRAS* mutations among the analyzed patients, corresponding to results from the literature [18], we decided not to perform *KRAS* analysis in the remaining patients.

Table 2 Worst adverse events per patient

	Grade 1 + 2 n (%)	Grade 3–4 n (%)	Grade 5 n (%)
Hematological toxicity			
Leucopenia	4 (8)	4 (8)	0
Neutropenia	4 (8)	8 (16)	0
Thrombocytopenia	0	0	0
Febrile neutropenia	–	1 (2)	0
Non-hematological toxicity			
Diarrhea	24 (48)	4 (8)	0
Nausea	35 (70)	0	0
Vomiting	15 (30)	1 (2)	0
Fatigue	36 (72)	5 (10)	0
Skin toxicity	31 (65)	1 (2)	0
Intestinal volvulus	0	0	1(2)
Pulmonary embolism	0	0	1(2)

Table 3 Efficacy of Cetiri as second-line therapy in GEC patients

	n (%)
Evaluable disease	48 (96)
Non-evaluable disease	2 (4)
Number of courses	
Total	478
Median	7 (1–46)
Response rate	
PR	7 (14)
SD	28 (56)
Median PFS	3.3 months (CI 1.9–4.4)
Median OS	5.5 months (CI 3.6–7.3)

Cetiri cetuximab and irinotecan, *GEC* gastro-esophageal cancer, *PR* partial response, *SD* stable disease, *PFS* progression-free survival, *OS* overall survival, *CI* confidence interval

Efficacy

In total, 478 treatment cycles were administered to 50 patients, with a median of seven cycles per patient (range 1–46) (Table 3). Forty-five patients were evaluable for response because treatment was stopped in five patients before the planned response evaluation after four courses. Reasons for early cessation were toxicity in two patients, death in two other patients (intestinal volvulus and pulmonary embolism), and one due to patient's request. The overall RR was 14%. Ten patients had progressive disease either before or at the time of their first evaluation. The median PFS was 3.3 months and OS was 5.5 months (Fig. 1). After a median follow-up of 29 months, one patient is continuing treatment without signs of progressive disease (PD) and two patients are still alive.
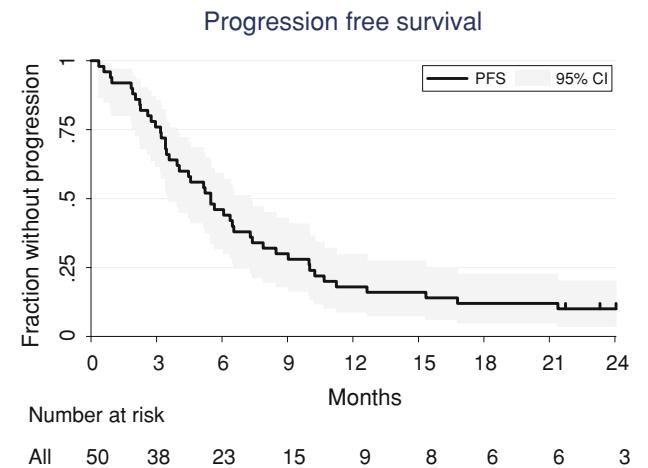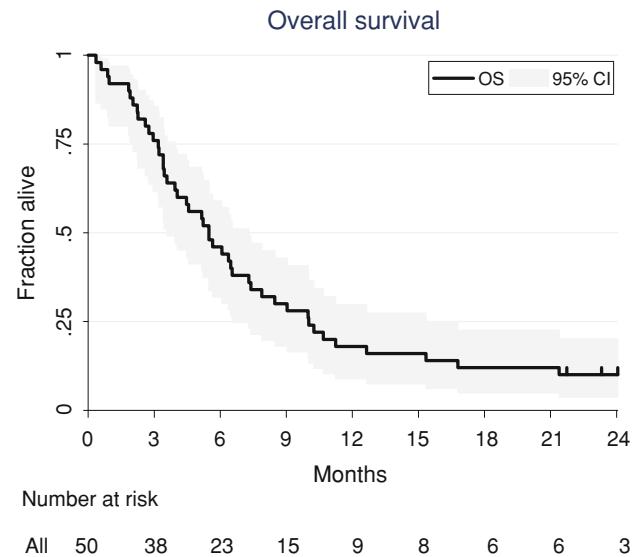

Fig. 1 Overall survival (*OS*) and progression-free survival (*PFS*). Kaplan–Meier curves of overall survival (median 5.5 months) and time to progression (median 3.3 months). *CI* Confidence interval

In the multivariate analysis PS = 1 and PS = 2 were significantly associated with a short OS. Furthermore, the development of rash was significantly associated with a prolonged OS (Table 4).

Discussion

After progression to first-line chemotherapy, patients with GEC have a dismal prognosis, with an expected OS of a few months. A subgroup of patients is, however, in a good PS at the time of progression and for these patients there is a need for effective second-line chemotherapy. At present, it is often daily clinical practice to offer second-line therapy to patients in a good PS, and 30–40% of all GEC patients receive second-line therapy after first-line progression

Table 4 Results of exploratory Cox-multivariate analysis of known and collected parameters for overall survival

Parameter	Hazard ratio (HR)	95% Confidence interval (CI)
Performance status 1	2.4*	1.12–5.32
Performance status 2	10.3*	2.45–43.64
WBC > 10 × 10^9/L	1.7	0.9–3.45
Platelets > 400 × 10^9/L	1.2	0.44–3.1
Rash	0.4*	0.17–0.81
Number of metastatic sites	1.6	0.77–3.17
TTP under first-line CT	1.0	0.99–1.0

* $p < 0.05$

[19–21]. Several phase II trials have investigated different drugs and combinations in the second-line setting, and promising agents such as irinotecan, taxanes, and platins have been tested [10, 11, 22, 23]. So far, no standard regimen has been established as second-line treatment. The need to find prognostic and predictive factors indicating who will benefit from both first- and second-line therapy is imperative. Recently analyses have been performed in order to clarify this question. Chau et al. [19] pooled data on 1080 patients from three randomized first-line trials and demonstrated that PS ≥ 2, the presence of liver and/or peritoneal metastases, and elevated alkaline phosphatase were prognostic factors correlated with poor outcome in the first-line setting. Subsequent analyses evaluating patients receiving different regimens of chemotherapy in the second-line setting have described PS ≥ 2, number of metastatic sites, short TTP under first-line chemotherapy, and different laboratory test results, such as low hemoglobinand elevated WBC or alkaline phosphatase as prognostic factors associated with overall survival [24–27].

Today the use of molecular targeting agents is a new challenge in modern cancer therapy and these agents may have a significant impact on the treatment of GEC patients in the future [28]. EGFR is over-expressed in many GEC patients and has, in some studies, been associated with a poor prognosis, underlining the significant role that the EGFR might have in human GEC biology. Preclinical trials in EGFR over-expressing gastric cancer cell lines and tumor xenografts have suggested an anti-tumor effect of cetuximab as a result of different intracellular and immunological mechanisms [29, 30]. Moreover, one recently described mechanism of resistance to cetuximab, mutation of the *KRAS* gene, seems to have a very low prevalence of 8% in GEC cancer [17, 31]. These findings are concurrent with the results seen in our study, where a *KRAS* mutation was found in only 10% of the 20 analyzed tumors.

As first-line therapy, cetuximab in combination with chemotherapy has been evaluated in phase II trials and has obtained promising results. In the Italian FOLCETUX study, Pinto et al. evaluated cetuximab in combination with irinotecan and 5-fluorouracil (5-FU) and recorded an RR of 44% (28–61%) and promising TTP and OS of 8 and 16 months, respectively, indicating potentially better efficacy than that achieved with irinotecan and 5-FU alone [32–34]. Recently other phase II studies have evaluated cetuximab in combination with either docetaxel and cisplatin, or oxaliplatin and 5-FU in the first-line setting and obtained similar results [35–37].

Unfortunately, limited data exist on the efficacy and predictors for the success of cetuximab as salvage therapy in pretreated patients. Stein et al. evaluated weekly irinotecan and cetuximab in 13 heavily pretreated GEC patients. In that study five patients obtained a PR, the overall disease control rate was 62%, and TTP and OS were 2.6 and 3.4 months, respectively [38]. Park et al. performed a retrospective analysis of 32 heavily pretreated patients mainly in PS 2–3. The disease control rate was 28.6%, PFS was 1.7 months, and OS was 3.2 months. In a multivariate analysis PS, skin rash, and metastatic sites were significantly associated with both PFS and OS [39]. Gold et al. [40] evaluated second-line cetuximab as monotherapy in patients with metastatic esophageal adenocarcinoma, but the trial failed to meet its primary endpoint of a median OS of 6.0 months. In a multivariate analysis, our study demonstrated that PS was a very strong prognostic factor. Both PS 1 and PS 2 were significantly associated with short overall survival (PS1: hazard ratio [HR] = 2.4; PS2: HR = 10.3) (Table 4). As a consequence we only recommend Cetiri for patients with PS ≤ 1. Furthermore, we found that the development of rash was significantly associated with OS. It is remarkable that developing a rash had a strong association with prolonged OS (HR = 0.4). Rash, on the basis of treatment with drugs directed against the EGFR, has also been described as a good prognostic factor in studies including patients with mCRC and pancreatic cancer. One could put forward a hypothesis whether GEC patients in the future could be selected for EGFR treatment based on the occurrence of rash after one or two courses of Cetiri. Surprisingly, our series failed to demonstrate that the number of metastatic sites, TTP under first-line chemotherapy, and different laboratory test results were prognostic factors. Cetiri was well tolerated and easily administered in the out-patient setting.

With a disease control rate of 70% and an RR of 14% the present consecutive series indicates that patients in a good PS and patients who develop a rash during treatment benefit from irinotecan and cetuximab every second week. However, these findings need validation in prospective trials.

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