original article

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Biweekly cetuximab and irinotecan as third-line therapy in patients with advanced colorectal cancer after failure to irinotecan, oxaliplatin and 5-fluorouracil

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Background: Standard weekly cetuximab and irinotecan (CetIri) is an effective regimen in heavily pretreated patients with advanced colorectal cancer (ACRC). Inspired by a pharmacokinetic study demonstrating no differences between weekly and biweekly cetuximab, we present the results of 74 consecutive patients treated with biweekly CetIri.
Methods: Biweekly CetIri schedule: cetuximab 500 mg/m^2, first course was given as a 120-min infusion followed 1 h later by irinotecan 180 mg/m^2 as a 30-min infusion. Subsequent courses of cetuximab were given in 60 min, immediately followed by irinotecan—resulting in an overall treatment time of 90 min.
Results: All patients had ACRC resistant to 5-fluorouracil and irinotecan and 95% to oxaliplatin. Median age was 63 years, median performance status was 0. Median duration of therapy was 4.3 months. Response rate was 25%. Median progression-free survival and overall survival were 5.4 months and 8.9 months, respectively, comparable to own historical controls receiving weekly CetIri. Grade 3–4 toxicity was rare (skin 7%, nail 3%, diarrhoea 10%, fatigue 3%, neutropenia 9%). One patient experienced severe allergic reaction.
Conclusion: Salvage therapy with simplified biweekly CetIri is a convenient, effective and well-tolerated regimen in heavily pretreated patients with ACRC. A confirmatory phase II study is ongoing.
Key words: advanced colorectal cancer, biweekly, cetuximab, irinotecan, third-line therapy

introduction

Until a decade ago, 5-fluorouracil (FU) and folinic acid (FA) was standard therapy in patients with advanced colorectal cancer (ACRC). FU/FA induced tumour regression in ~20% of the patients with ACRC, prolonged survival from median 6 to 12 months and improved quality of life [1]. The introduction of irinotecan and oxaliplatin, as first- and second-line therapy, enhanced these results significantly [1–4]. First-line combination chemotherapy raises response rates to almost 50% and lengthens progression-free survival (PFS) from 4–6 months to 6–8 months [1, 2]. Second-line therapy after first-line combination therapy generates response rates of 5%–20%, increases PFS to 4–6 months [3–6] and also adds to a prolonged overall survival (OS) but no chemotherapy regimen has shown activity in patients with ACRC resistant to oxaliplatin and irinotecan [7]. Presently, cetuximab is the most promising drug in heavily pretreated patients. Cetuximab is an IgG-1 mAb that binds to the epidermal growth factor receptor (EGFR). Preclinical and clinical studies have shown that cetuximab (Erbitux®) has activity as a single-agent and synergistic activity in combination with chemotherapy [7–11]. Compared with best supportive care, cetuximab significantly prolong OS from median 4.6 to 6.1 months and also improve quality of life [12]. In addition, the combination of cetuximab and irinotecan (CetIri) significantly increases response rate from 11% to 23% and prolong PFS from median 1.5 to 4.5 months compared with cetuximab monotherapy [10]. Since January 2005, CetIri has been offered to Danish patients with ACRC after failure of FU/FA, irinotecan and oxaliplatin, and each case approved by the Danish Health Authorities [7, 13]. Up till September 2005, 65 consecutive patients received standard weekly CetIri at three University Hospitals. Cetuximab was administered with an initial loading dose of 400 mg/m^2 as a 120-min infusion and subsequently weekly as 250 mg/m^2 in 60 min. Irinotecan 180 mg/m^2 was administered every second week starting 1 h after completion of cetuximab. Efficacy and toxicity have previously been reported and were very similar to the results in the BOND I trial [7, 10].

Many chemotherapy regimens are administered every second week and therefore it would be more convenient both for the patient and for the treating institution if cetuximab could be administered every 2 weeks. A pharmacokinetic study by Tabernero et al. [14] showed no major differences between cetuximab 250 mg/m^2 every week and cetuximab 500 mg/m^2

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every second week and on the basis of these data we have eased the administration of CetIri and here we report the results of the first 74 patients with ACRC receiving biweekly CetIri.

materials and methods

The initial 74 consecutive patients receiving CetIri every second week at two University Hospitals are the subject of this study.

The administration of CetIri was gradually simplified. The first few among the 74 patients began treatment every second week if computed tomography (CT) scan after 6 weekly courses showed no sign of progressive disease. However, within 3 months, cetuximab was routinely administered every second week as 500 mg/m^2. The first course was infused in 120 min followed 1 h later by irinotecan 180 mg/m^2 as a 30-min infusion. Subsequent courses of cetuximab was infused in only 60 min, immediately followed by irinotecan—resulting in a total treatment time of 90 min every second week. Patients received premedication with antihistamine (e.g. 50 mg diphenhydramine hydrochloride i.v.) to minimise the risk of infusion-related reactions associated with cetuximab. Before cetuximab infusion, patients also received antiemetics with oral prednisolone 100 mg and granisetron 1 mg i.v. Immediately before irinotecan, in order to prevent irinotecan-associated acute cholinergic syndrome, 0.25 mg atropin was given s.c. or as a slow i.v. infusion.

All patients had histologically confirmed nonresectable colorectal adenocarcinoma resistant to therapy with FU/FA (all patients), irinotecan (all patients) and oxaliplatin (95% of patients). Oxaliplatin was in all cases combined with a fluoropyrimidine regimen, the Nordic regimen (FLOX) [15], an infusional regimen (FOLFOX) or oral therapy with capecitabine (XELOX). As first-line therapy irinotecan was also combined with a fluoropyrimidene but as second-line therapy single-agent irinotecan was often administered. EGFR expression was not determined [7, 11]. Tumour response was assessed on a CT scan by the investigators after 6–8 weeks and then every 8 weeks according to the Response Evaluation Criteria in Solid Tumors. Therapy was continued until disease progression or unacceptable toxicity. Pretreatment evaluation included a medical history, physical examination, complete blood count, chemistry profile of renal and liver function (creatinine, ALAT, alkaline phosphatase and bilirubin) and radiological (CT scan or magnetic resonance scan) assessment of tumour. A complete blood count was obtained before each irinotecan infusion.

Toxicity was evaluated and recorded before each course according to Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. In the case of CTCAE grade 3 or 4 drug doses were reduced by 25% in the subsequent treatment cycles.

Data were recorded and analysed in a Medlog® database. Nonparametric statistics were applied. All median values are followed by range in brackets. PFS was calculated as the period from the first infusion with cetuximab to the first observation of disease progression, to death from any cause or the most recent assessment. OS was calculated as the period from the first infusion of cetuximab until death from any cause.

According to National Guidelines, an expert panel appointed by the National Board of Health must approve therapy with CetIri. Therefore, we also calculated the delay time as, the period from the date of indication for CetIri to first infusion of CetIri. Data were updated on 1 May 2007. Both PFS and OS were estimated by the Kaplan–Meier method.

results

patient characteristics

Patient characteristics are listed in Table 1 and compared with a historical control group, 65 patients receiving weekly CetIri at our institutions [7]. Four patients received adjuvant therapy with oxaliplatin (FOLFOX or XELOX). Fifty-seven patients received irinotecan as second- or third-line therapy, and in 33 patients, irinotecan was given as single agent 350 mg/m^2 every third week (Table 1).

Seventy-four consecutive patients were treated from November 2005 to December 2006. Median age was 63 years

Table 1. Characteristics for patients treated with weekly cetuximab and irinotecan (CetIri) or biweekly CetIri at the same institutions

Characteristic	Weekly CetIri 250 mg/m^2	Biweekly CetIri 500 mg/m^2
Inclusion periods	January 2005 to September 2005	November 2005 to December 2006
Numbers	65	74
WHO performance status		
0	29	39
1	24	29
2	9	5
3	3	1
Age, years (median, range)	57 (29–77)	63 (23–78)
Sex (male/female)	40/25	46/28
Primary tumour site: colon/rectum	41/24	55/19
Synchronous metastases, *n* (%)	39 (60)	48 (65)
Metachronous metastases, *n* (%)	26 (40)	26 (35)
Time from primary diagnosis to metachronous metastasis, months (median, range)	17 (3–78) (*n* = 26)	17 (6–57) (*n* = 26)
Prior therapy with oxaliplatin	65 (100%)	70 (95%)
Prior therapy with irinotecan	65 (100%)	74 (100%)
Duration of first-line therapy, months (median, range)	5.4 (1.0–14.3) (*n* = 65)	5.3 (0.5–16.5) (*n* = 69)
Response rate (95% CI)	44%	51%
Duration of second-line therapy, months (median, range)	4.0 (1.4–9.4) (*n* = 63)	3.5 (0.5–27.0) (*n* = 67)
Response rate (95% CI)	19%	9%

WHO, World Health Organization; CI, confidence interval.

(23–78), 46 patients were males and the location of the primary tumour was colon in 55 and rectum in 19 patients. Forty-eight patients had synchronous metastases. Twenty-six patients had metachronous metastases that were diagnosed median 17 months (6–57) after the primary diagnosis. Patients received therapy with irinotecan and cetuximab for median 16 months (3–60) after the primary diagnoses of nonresectable disease (Table 2). Most patients were in a good baseline Eastern Cooperative Oncology Group performance status (PS) with 39 patients in PS = 0 and 29 patients in PS = 1.

efficacy of irinotecan and cetuximab

Efficacy data are listed in Table 2 and compared with 65 patients receiving weekly CetIri at our institutions [7]. The median duration of therapy with cetuximab was 4.3 months (0.5–12.9) and median number of cetuximab infusions every second week was 8 (1–26). One patient had complete response and 18 patients had partial response resulting in an overall response rate of 25.7% [95% confidence interval (CI) 16.2% to 37.2%]. In addition, 38 patients had stable disease resulting in an overall disease control rate of 77.0% (65.8–85.0).

Median PFS was 5.4 months (95% CI 4.7–6.5 months) with an actuarial 78% without progression at 3 months and 46% at 6 months (Figure 1). Median OS was 8.9 months (95% CI 7.0–10.5 months) with an actuarial 67% alive at 6 months and 34% at 12 months (Figure 1). PS was the only covariate of importance for outcome, patients with PS = 0 and PS = 1–3 had a median OS of 10.0 and 7.6 months, respectively.

Patients without skin toxicity ($n = 11$) had a significantly shorter PFS (3.4 months versus 6.2 months; $P = 0.004$) and OS (6.3 versus 9.9 months; $P = 0.004$) than patients with rash any grade and none of the 11 patients without rash obtained tumour regression.

Table 2. Efficacy of treatment with weekly cetuximab and irinotecan (CetIri) or biweekly CetIri in two consecutive periods at the same institutions

Characteristic	Weekly CetIri 250 mg/m^2	Biweekly CetIri 500 mg/m^2
Number	65	74
Time from nonresectable disease to 'indication for cetuximab', months (range)	20 (5–58)	16 (3–60)
Median 'delay' time, time from date of indication to the first infusion of CetIri, weeks (range)	6 (0–88)	6 (0–36)
Median number of weeks with cetuximab (range)	16 (1–51)	17 (2–52) (8 biweekly courses)
Response rate		
Complete response (CR)	0	1 (1%)
Partial response (PR)	12 (19%)	18 (24%)
Stable disease (SD)	31 (47%)	38 (52%)
Disease control (CR + PR + NC)	43 (66%)	57 (77%)
Progression (PD)	15 (23%)	13 (18%)
Not evaluable	7 (11%)	4 (5%)
PFS, months (95% CI)	5.4 (4.6–6.1)	5.4 (4.7–6.5)
OS, months (95% CI)	10.4 (7.2–13.1)	8.9 (7.0–10.5)

CI, confidence interval; PFS, progression-free survival; OS, overall survival.

toxicity

Toxicity data are listed in Table 3 and compared with 65 patients receiving weekly CetIri at our institutions [7].

Toxicity was modest. CTCAE toxicity grades 2 and 3–4 are shown in Table 3. Diarrhoea grade 3 was seen in 10% of the patients and skin toxicity in 7%. Only one patient had severe allergic reaction. No patient was lost due to toxicity.

discussion

The combination of cetuximab and irinotecan is an effective regimen in heavily pretreated patients with ACRC [10, 11]. Since January 2005, this combination has been offered to Danish patients with ACRC pretreated with FU, oxaliplatin and irinotecan. According to a national health programme, the treatment must be approved by an expert panel appointed by the National Board of Health that subsequently finances the cost of treatment [7]. This health programme has had a major impact on the management of cancer patients in Denmark and has accelerated the introduction and implementation of new regimens.

On the basis of previous studies, it is recommended that cetuximab is administered weekly. We have previously

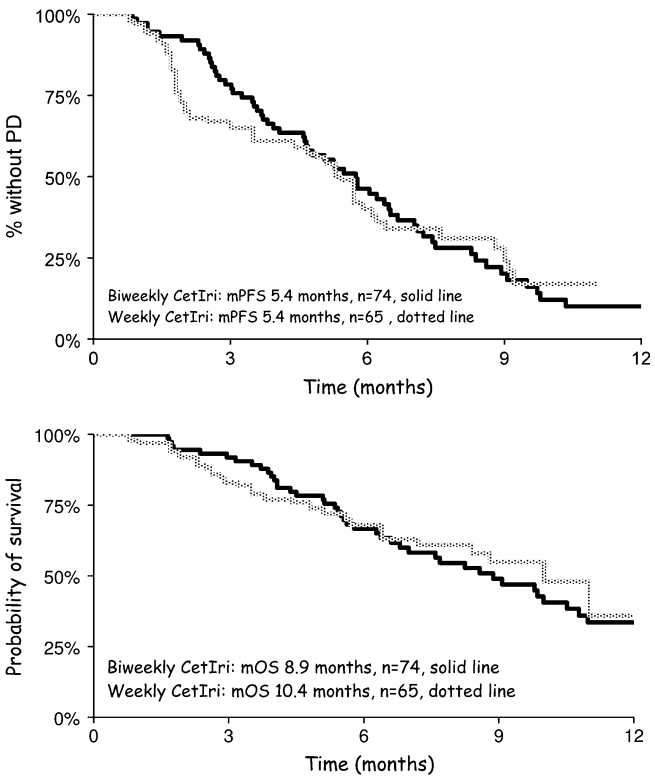

Figure 1. Kaplan–Meier curves of progression-free survival for 74 patients treated with biweekly cetuximab and irinotecan (CetIri) and 65 patients treated with weekly CetIri and Kaplan–Meier curves of overall survival for 74 patients treated with biweekly CetIri and 65 patients treated with weekly CetIri.

Table 3. Toxicity of treatment with weekly cetuximab and irinotecan (CetIri) or biweekly CetIri in two consecutive periods at the same institutions

Toxicity	Weekly CetIri 250 mg/m^2		Biweekly CetIri 500 mg/m^2	
	Grade		Grade	
	2	3 or 4	2	3 or 4
Skin (%)	25	8	40	5
Nail (%)	11	3	13	3
Diarrhoea (%)	22	10	9	9
Nausea (%)	11	3	12	0
Vomiting (%)	5	3	7	0
Fatigue (%)	30	8	36	4
Alopecia (%)	10	–	11	–
Neutropenia (%)	6	4	3	7
Thrombocytopenia (%)	3	0	3	0
Anaphylactic reaction (%)		4.6	1.4	1.4
Death, $n = 1$ (%)		1.5[a]		0

[a]One patient died of neutropenia infection after 11 courses of cetuximab and 3 courses of irinotecan.

reported the results of 'third-line' therapy with irinotecan and standard weekly cetuximab [7]. In the initial 65 treated Danish patients, we found efficacy and toxicity very similar to the data presented in the pivotal BOND I study [10].

Inspired by a pharmacokinetic and pharmacodynamic study which showed no major differences between weekly cetuximab 250 mg/m^2 and biweekly cetuximab 500 mg/m^2 [14], we have subsequently simplified the administration of CetIri. The first course of cetuximab is infused in 120 min followed 1 h later by irinotecan 180 mg/m^2 as a 30-min infusion. However, subsequent courses of cetuximab are infused in only 60 min and immediately after, without the recommended 1-h pause, irinotecan is infused in 30 min—resulting in a total treatment time of only 90 min every second week which is more convenient for the patient.

Our two groups of patients are comparable as they are treated in two immediate consecutive periods in the same regions recruiting patients and with the same procedures for establishing the indication for treatment. Patients were treated in the same few institutions with the same staff and treatment procedures.

The groups were comparable regarding age, sex, the primary location of the tumour, numbers of patients with synchronous metastases and time from primary diagnosis to development of metachronous metastatic disease. Previous treatment intensity, duration of first- and second-line therapy and median 'delay' time from the treating physician would have given the first course of cetuximab till it actually was administered was comparable.

Efficacy data for weekly and biweekly CetIri were very similar. The median duration of therapy was 4.7 versus 4.3 months; response rates 19% versus 25%; median PFS 5.4 versus 5.3 months and median OS 10.4 versus 8.9 months, respectively.

In the cohort receiving weekly cetuximab, we found an excellent correlation between severity of skin rash and OS [7] but in patients receiving biweekly cetuximab this correlation was less clear. Patients with rash any grade had a longer OS than patients without rash but there was no correlation between severity of rash and OS. Several studies have shown a clear correlation between severity of skin rash and efficacy of CetIri [7, 10, 11]. A recent phase III study presented at American Society of Clinical Oncology 2007 showed that administration of tetracycline significantly reduced severity (but not incidence) of skin rash [16]. In our institutions, nurses and physicians have a huge experience in the treatment of cetuximab-related skin toxicity and often the patients receive instant therapy (systemic tetracycline and/or different lotions) at the first appearance of skin rash. These therapies have definitely reduced the severity of skin rash and this might explain why we found no correlation between severity of skin rash and OS.

Toxicity data in the cohorts are also similar and comparable to the data from the pivotal BOND study [10] and to other studies where cetuximab is administered on a weekly basis [11].

We conclude that salvage therapy with simplified biweekly CetIri is a convenient, effective and well-tolerated regimen in patients with ACRC resistant to FU, Iri and oxaliplatin. Simplified CetIri does not increase the risk of allergic reactions or other side-effects.

A confirmatory Danish phase II study aiming to include >125 patients is ongoing.

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