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Adding cetuximab to capecitabine plus oxaliplatin (XELOX) in first-line treatment of metastatic colorectal cancer: a randomized phase II trial of the Swiss Group for Clinical Cancer Research SAKK

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Background: To determine the activity and tolerability of adding cetuximab to the oxaliplatin and capecitabine (XELOX) combination in first-line treatment of metastatic colorectal cancer (MCC).

Patients and methods: In a multicenter two-arm phase II trial, patients were randomized to receive oxaliplatin 130 mg/m^2 on day 1 and capecitabine 1000 mg/m^2 twice daily on days 1–14 every 3 weeks alone or in combination with standard dose cetuximab. Treatment was limited to a maximum of six cycles.

Results: Seventy-four patients with good performance status entered the trial. Objective partial response rates after external review and radiological confirmation were 14% and 41% in the XELOX and in the XELOX + Cetuximab arm, respectively. Stable disease has been observed in 62% and 35% of the patients, with 76% disease control in both arms. Cetuximab led to skin rash in 65% of the patients. The median overall survival was 16.5 months for arm A and 20.5 months for arm B. The median time to progression was 5.8 months for arm A and 7.2 months for arm B.

Conclusion: Differences in response rates between the treatment arms indicate that cetuximab may improve outcome with XELOX. The correct place of the cetuximab, oxaliplatin and fluoropyrimidine combinations in first-line treatment of MCC has to be assessed in phase III trials.

Key words: capecitabine, cetuximab, metastatic colorectal cancer, oxaliplatin, randomized phase II

introduction

The treatment of advanced colorectal cancer has made considerable progress in recent years. The newest developments are monoclonal antibodies (MoABs) such as cetuximab and bevacizumab, which have shown activity in different disease settings [1–3].

Cetuximab (Erbitux™ Merck KGaA, Darmstadt, Germany/ Imclone Systems Inc., Somerville, NJ) is an immunoglobulin G_1 MoAB that binds to the epidermal growth factor receptor (EGFR) with high specificity and a higher affinity than its natural ligands EGF and transforming growth factor-α. Thus, downstream effects of EGFR activation such as proliferation, angiogenesis or suppression of cell death are inhibited [4]. Clinical studies in colorectal cancer have shown cetuximab to induce responses in irinotecan-refractory disease [1, 3]. Comparative studies on cetuximab in the first-line setting in combination with oxaliplatin and capecitabine have not been published so far.

We carried out a randomized phase II trial of adding cetuximab to first-line oxaliplatin plus capecitabine (XELOX) [5, 6]. The rationale of this study was to assess the activity and the safety of the combination and to select the more promising of the two treatment arms under consideration. Treatment was limited to six chemotherapy cycles since there seemed to be no proven benefit of continuing chemotherapy until progression in advanced colorectal cancer at the time the study was planned [7].

methods

eligibility and patient evaluation

Eligible patients had histologically or cytologically confirmed advanced or metastatic adenocarcinoma of the colon or the rectum, which was not considered amenable to surgical treatment. Other eligibility criteria were measurability of tumor lesions (≥20 or ≥10 mm if the computed

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tomography slice thickness was ≤5 mm), no chemotherapy pretreatment of metastatic cancer, age 18 years or older, World Health Organization performance status of 0 or 1 and adequate organ function. In addition, immunohistochemical evidence of EGFR expression measured semiquantitatively (>0 on a scale of 0, 1+, 2+ or 3+) in a single reference laboratory was required. These measurements were carried out and graded using a now commercially available kit (EGFRpharmDx; Dako, Carpinteria, CA) according to the manufacturer's instructions. This requirement was lifted after it became evident that EGFR positivity is not predictive for response to cetuximab treatment [8] (last four patients). The creatinine clearance had to be ≥50 ml/min. Stratification factors for randomization were performance status (0 versus 1), prior adjuvant chemotherapy (yes versus no), a tumor-free interval of >6 months (yes versus no) and institution. The protocol was approved by local ethics review boards of all participating institutions, and all patients gave written informed consent before enrollment.

Pretreatment evaluation included a complete medical history and physical examination, a complete blood count, chemistry profile and carcinoembryonic antigen (CEA) measurement and a radiological tumor parameter assessment. A complete blood count was obtained weekly for the first two treatment cycles; it was then continued thrice weekly for patients in arm A, and weekly throughout the treatment phase for patients in arm B. A serum chemistry profile, CEA measurement, physical examination and toxicity assessment were done before the start of each 3-week cycle. Patients had radiological tumor parameter assessment every 9 weeks during treatment and every 12 weeks thereafter. Tumor response classification was on the basis of Response Evaluation Criteria in Solid Tumors (RECIST) [9] criteria.

response assessment

An independent response review was conducted by two radiologists and one medical oncologist. Only the images of patients who had progressed at first follow-up (9 weeks) or had discontinued study treatment before the first follow-up were excluded for review. Thus, images of 64 from the 74 patients were reviewed. The reviewers were blinded to the treatment arm and to the investigator's initial assessment.

assessment of toxicity

Toxic effects were assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 (publish date 10 June 2003).

treatment

This trial was conducted at nine centers. Patients were registered at the Coordinating Center before starting treatment. Patients received oxaliplatin 130 mg/m^2/day on day 1, given as a 2-h infusion in 250 ml of dextrose 5% repeated every 3 weeks. Capecitabine was administered orally at a dose of 1000 mg/m^2 twice daily as an intermittent regimen in 3-week cycles (2 weeks of treatment followed by a 1-week rest period). For practical reasons, capecitabine doses were rounded to the nearest dose that could be administered with 500- and 150-mg tablets of the drug. Capecitabine was given ∼12 h apart and taken orally with water within 30 min after ingestion of food. Cetuximab was administered at an initial dose of 400 mg/m^2 followed by weekly infusions of 250 mg/m^2 (arm B). Prophylaxis with an antihistaminic drug was recommended. Treatment was continued up to a maximum of six cycles or until disease progression, unacceptable adverse effects, surgery or withdrawal of consent by the patient. Second-line treatment was not predefined. Chemotherapy drugs were interrupted in case of grade ≥2 nonhematological toxicity and were not resumed until the adverse effect improved to grade ≤1. Capecitabine and oxaliplatin dose reductions were required after grade 3–4 toxicity or repeated occurrence of grade 2 toxicity. Capecitabine dose was modified for renal impairment according to the recommendations of the manufacturer. Oxaliplatin was modified for peripheral neuropathy according to the recommendations of the manufacturer. Cetuximab dose reductions were required after repeated occurrence of grade 3–4 toxicity. A treatment delay of >3 weeks (2 weeks for cetuximab) was considered as treatment failure (off treatment).

statistical analysis

The randomized two-arm phase II design was used to select the more promising schedule of the two in terms of response [10]. In this design, the schedule with the higher response rate is to be selected for future phase III studies, irrespective of the difference. To have at least 90% probability of selecting the truly better schedule when the absolute difference in true response proportions (complete response + partial response) is ≥15%, 37 patients are needed for each arm. Formal statistical comparisons between the arms were not legitimate and not planned in this phase II trial. Time to treatment failure was measured from randomization to treatment stop from any cause or until progression, time to progression from randomization to progression and overall survival from randomization to death. Time to event data were analyzed by the Kaplan–Meier method. Confidence intervals (CIs) for response rates and selected toxicity rates were calculated by the Clopper–Pearson method [11]. All treated patients were included in the evaluation of the primary end point response rate. Statistical analyses were carried out using SAS 9.1 (SAS Institute Inc., Cary, NC), S-PLUS 7.0 (Insightful Corporation, Seattle, WA) and StatXact 5.0 (Cytel Software Corporation, Cambridge, MA).

results

patients and treatment

From June 2004 until October 2005, a total of 74 patients were randomized to one of the two treatment arms. All patients were eligible. Table 1 lists the demographic data and baseline disease and pretreatment characteristics for all patients. Patients were well balanced for these characteristics.

Sixty-four percent and 68% of the patients completed the planned six treatment cycles. Reasons for not completing protocol treatment were disease progression, unacceptable toxicity, resection of liver metastases and death (three in arm A: ischemic colitis, tumor progression, *Escherichia coli* sepsis). The median number of 3-week cycles received was six (range 1–6) for arm A and six (range 2–6) for arm B. The median dose intensity for capecitabine was 1914 mg/m^2 for arm A and 1964 mg/m^2 for arm B. The median dose intensity for oxaliplatin was 127 mg/m^2 for arm A and 129 mg/m^2 for arm B.

toxicity

The incidence of worst grade 1/2 and 3/4 toxicity per patient is summarized in Table 2. Only skin toxicity was clearly more frequent in the cetuximab-containing treatment arm. No patient refused treatment because of skin toxicity. Adding cetuximab to XELOX did not increase the risk of hand–foot and nail toxicity on a clinically relevant scale.

activity end points

The best tumor responses after external review and radiological confirmation are shown in Table 3. Partial response rates were 14% (95% CI: 5%–29%) in arm A and

Table 1. Patient and disease characteristics

	CAPOX ($n = 37$)		CAPOX + Cetuximab ($n = 37$)	
	n	%	*n*	%
Age				
Median (range)	63 (47–80)		60 (37–81)	
Sex				
Female	16	43	14	38
Male	21	57	23	62
WHO performance status				
0	21	57	22	59
1	16	43	15	41
Metastases				
Metachronous	7	19	6	16
Synchronous	30	81	31	84
Previous adjvant chemotherapy	7	19	4	11
Site of primary				
Colon ascendens	10	27	6	16
Colon descendens/sigmoideum	11	30	18	49
Colon transversum	2	5	0	–
Rectum	16	43	15	41
Liver metastases	32	86	33	89
EGFR positive	36	97	34	94

WHO, World Health Organization; EGFR, epidermal growth factor receptor.

Table 2. Worst toxicity per patient

	CAPOX ($n = 37$)		CAPOX + Cetuximab ($n = 37$)	
	% grade 1/2	% grade 3/4	% grade 1/2	% grade 3/4
Nausea	46	3	51	5
Vomiting	24	3	24	5
Mucositis/stomatitis	19	3	14	8
Diarrhea	41	16	32	22
Anorexia	32	–	43	5
Febrile neutropenia	–	–	–	–
Fever	16	3	19	–
Fatigue	51	3	51	14
Skin rash	5	–	57	8
Alopecia	5	–	5	–
Hand–foot syndrome	24	5	32	3
Nail changes	–	–	3	–
Rash	3	–	32	8
Skin	8	–	78	16
Allergic reaction	3	–	–	3
Oxaliplatin-related peripheral neuropathy	73	3	86	3
Anemia	86	3	68	–
Leucopenia	30	3	32	–
Neutropenia	30	3	22	–
Thrombocytopenia	57	11	62	3

41% (95% CI: 25%–58%) in arm B. Stable disease has been observed in 62% and 35% of the patients. The reviewed response rates (all PR) at 9 weeks (first per protocol response evaluation) were 27.0% (95% CI: 14%–44%) in arm A and 43.2% (95% CI: 27%–61%) in arm B. The reviewed response rates at 18 weeks were 21.6% (95% CI: 10%–38%) and 43.2% (95% CI: 27%–61%). If all reviewed responses were considered without the requirement for response confirmation 4 weeks after the criteria for response were first met, the respective overall response rates were 35.1% (95% CI: 20%–52%) and 54.0% (95% CI: 37%–71%).

Table 3. Best tumor response after review and radiological confirmation

	XELOX ($n = 37$)		XELOX + Cetuximab ($n = 37$)	
	n	%	*n*	%
PR	5	14	15	41
SD	23	62	13	35
PD (before or at 18 weeks)	6	16	7	19
Not reviewed				
Treatment stop before 18 weeks	2	5	0	0
Missing images	1	3	2	5

SD, stable disease; PD, progressive disease; XELOX, adding cetuximab to the oxaliplatin and capecitabine.

The median time to treatment failure (defined as stop of treatment due to any reason, progression or death) was 5.7 months (95% CI: 4.5–7.6) for arm A and 7.2 months (95% CI: 4.4–7.9) for arm B. The median time to progression was 5.8 months (95% CI: 5.0–8.3) for arm A and 7.2 months (95% CI: 6.0–8.4) for arm B (Figure 1). The median overall survival was 16.5 months (95% CI: 14.3–27.0+) for arm A and 20.5 months (95% CI: 15.5–27.2) for arm B (Figure 2). The median follow-up time for living patients was 17.2 months (range 7.1–27.0).

Ten patients in arm A and 14 patients in arm B had metastases confined to the liver. On four patients in each treatment arm, surgery of liver metastases could be carried out.

discussion

This is the first published trial to combine cetuximab with XELOX [5, 6] in the first-line treatment of metastatic colorectal cancer. Recently presented phase III trials have shown comparable activity and balanced toxicity of XELOX and standard FOLFOX-4 or FOLFOX-6 [12–14]. XELOX might be more convenient for patients because of the use of an oral fluoropyrimidine instead of infusional fluorouracil [14, 15]. Thus, XELOX is an interesting combination partner for other active drugs such as MoABs. Our study shows that the addition of cetuximab increases the activity of XELOX without the increase in severe toxicity. One concern was that this combination might lead to severe mucocutaneous side effects since both components are associated with this type of toxicity. The results of our study did not substantiate this concern. However, the toxicity profile of the combination was dominated by skin eruptions typical for the use of EGFR antibodies. No patient refused treatment because of skin toxicity. Clearly, research on the management of this type of skin toxicity has to be intensified since it is the major obstacle for the clinical use of EGFR antibodies.

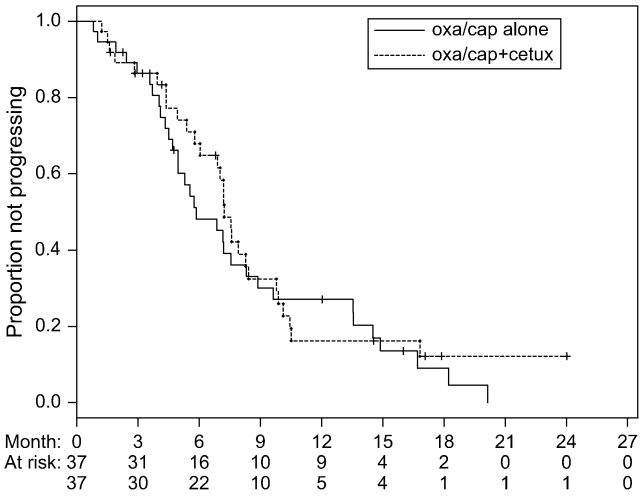

Figure 1. Time to tumor progression.

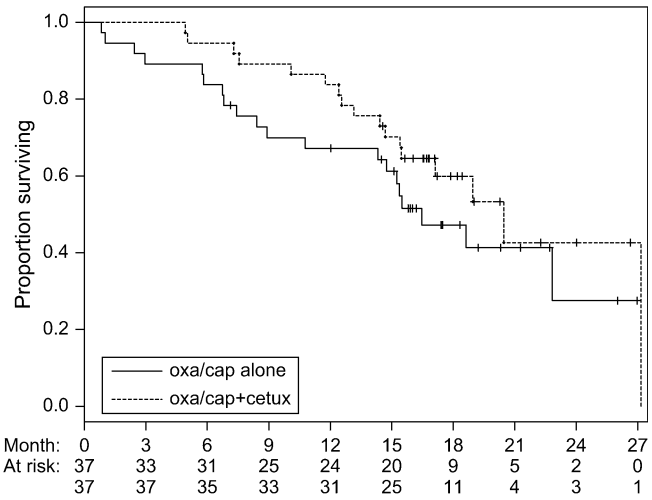

Figure 2. Overall survival.

So far, only one trial has been presented that has used cetuximab in combination with a standard oxaliplatin combination in a comparative setting in first-line colorectal cancer. Bokemeyer et al. [16] have carried out a randomized phase II study comparing FOLFOX-4 alone or in combination with cetuximab. Cetuximab increased the overall response rate from 35.7% to 45.6%. The toxicity pattern differed only in respect to the typical cetuximab-associated skin toxicity, which occurred in 14.1% of the patients in grade 3 intensity. This is comparable to the 16% skin toxicity observed in our trial.

Adding cetuximab to XELOX increased the response rates from 14% to 41% in our study. While the response rate of the cetuximab combination is comparable with the Bokemeyer trial, the low response rate of 14% in the XELOX arm is of concern. Response assessment was strictly reviewed in our study, but recent results from a large international randomized phase III study demonstrated a 37.1% response rate also with independent review [13, 14]. Our original publication on the XELOX regimen reported a 49% response rate without independent review, while the respective rate was 55% in the paper of Cassidy et al. with independent review [5, 6]. On the other hand, Tabernero described a reviewed response rate of 72% with the cetuximab plus FOLFOX-4 combination as compared with 45.6% in the Bokemeyer trial [16, 17], demonstrating a wide range of possible outcomes in seemingly similar settings. The low response rate in our XELOX arm is not explained by early disease progression, since additional 62% of the patients in arm A experienced disease stabilization. Thus, the disease control rate of 76% in our study population is comparable to other trials [5, 6, 17].

The treatment in our study was limited to six cycles resulting in a treatment duration of 18 weeks or 4.5 months. The median time to progression was 5.8 months for arm A and 7.2 months for arm B suggesting a short response duration off treatment in most of these patients. This leads to the question whether longer treatment duration could have improved response stability and time to progression. There are several suggestions that palliative chemotherapy in advanced colorectal cancer does not have to be continued until tumor progression [7, 18, 19], while the recent analysis from the OPTIMOX2 trial has shown prolonged overall survival with maintenance chemotherapy [20]. Some patients in our study were rapidly deteriorating after six treatment cycles despite good initial tumor response and one may speculate that treatment refractory liver failure due to very rapid tumor progression could have been prevented by prolonged treatment administration.

The results of various studies indicate now that adding cetuximab to standard oxaliplatin combinations leads to higher response rates as reported with the respective oxaliplatin combination alone [17, 16]. Thus, the advantage of the cetuximab plus oxaliplatin combination seems to be most obvious in the situation of potentially resectable metastases from colorectal cancer, where rapid and extensive tumor shrinkage is the primary treatment goal [21]. Whether cetuximab and oxaliplatin are combined with oral capecitabine or continuous infusion fluorouracil will remain a matter of preference rather than activity in view of recent results [12–14]. Another important choice in this disease setting is whether to use cetuximab or bevacizumab in combination with XELOX or FOLFOX. This answer will come from randomized phase III studies directly comparing a cetuximab with a bevacizumab treatment option. Interestingly, despite significantly prolonging survival with first-line irinotecan combinations in colorectal cancer, so far bevacizumab has failed to improve the activity of XELOX in terms of tumor response rates [13, 14]. Recent data indicate that tumor response to EGFR antibodies is restricted to tumors with nonmutated KRAS [22]. If this finding is confirmed in prospective studies, it will be possible to target treatment with cetuximab more selectively.

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