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Capecitabine and irinotecan with and without bevacizumab for advanced colorectal cancer patients

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Abstract

AIM: To investigate the efficacy and safety of capecitabine plus irinotecan ± bevacizumab in advanced or metastatic colorectal cancer patients.

METHODS: Forty six patients with previously untreated, locally-advanced or metastatic colorectal cancer (mCRC) were recruited between 2001-2006 in a prospective open-label phase Ⅱ trial, in German community-based outpatient clinics. Patients received a standard capecitabine plus irinotecan (CAPIRI) or CAPIRI plus bevacizumab (CAPIRI-BEV) regimen every 3 wk. Dose reductions were mandatory from the first cycle in cases of > grade 2 toxicity. The treatment choice of bevacizumab was at the discretion of the physician. The primary endpoints were response and toxicity and secondary endpoints included progression-free survival and overall survival.

RESULTS: In the CAPIRI group *vs* the CAPRI-Bev group there were more female than male patients (47% *vs* 24%), and more patients had colon as the primary tumor site (58.8% *vs* 48.2%) with fewer patients having sigmoid colon as primary tumor site (5.9% *vs* 20.7%). Grade 3/4 toxicity was higher with CAPIRI than CAPIRI-Bev: 82% *vs* 58.6%. Partial response rates were 29.4% and 34.5%, and tumor control rates were 70.6% and 75.9%, respectively. No complete responses were observed. The median progression-free survival was 11.4 mo and 12.8 mo for CAPIRI and CAPIRI-Bev, respectively. The median overall survival for CAPIRI was 15 mo (458 d) and for CAPIRI-Bev 24 mo (733 d). These differences were not statistically different. In the CAPIRI-Bev, group, two patients underwent a full secondary tumor resection after treatment, whereas in the CAPIRI group no cases underwent this procedure.

CONCLUSION: Both regimens were well tolerated and offered effective tumor growth control in this outpatient setting. Severe gastrointestinal toxicities and thromboembolic events were rare and if observed were never fatal.

Key words: First-line therapy; Metastatic colorectal cancer; Bevacizumab; Capecitabine; Irinotecan; Tumor response

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INTRODUCTION

Until relatively recently, the anti-metabolite 5-fluorouracil (5-FU) was the only effective first-line treatment for metastatic colorectal cancer (mCRC). Subsequent attempts to improve its efficacy centered on its co-administration with leucovorin (LV)[1]. An alternative approach to optimize 5-FU-based therapy was made possible with the advent of oral fluoropyrimidine derivatives. Capecitabine is such an oral FU pro-drug specifically designed to deliver 5-FU to tumor cells with predictable bioavailability and sustained exposure[2-4]. Capecitabine has shown promising results and clinically meaningful safety advantages over 5-FU/LV, although with no improved efficacy[5-8]. Its oral administration makes it more convenient, and its proven safety might increase its appeal to patients who have expressed a preference for oral cytotoxic therapy over intravenous regimens (iv)[9,10].

Additionally, over the last decade improved survival has been achieved with the arrival of new agents, including irinotecan and oxaliplatin[11,12]. Two large randomized clinical trials have shown that irinotecan combined with 5-FU/LV (FOLFIRI or bolus IFL) significantly improved response rates, time to progression and overall survival[12,13]. Based on data from these, and other trials[12-16] the combination regimens FOLFIRI and oxaliplatin/5-FU/LV (FOLFOX) replaced 5-FU/LV as a standard treatment of mCRC.

Thus, following promising data from phase Ⅰ/Ⅱ trials in colorectal cancer (CRC), interest in the combination of capecitabine with irinotecan (CAPIRI) as an equally effective, more convenient alternative to the FOLFIRI and FOLFOX regimens has grown[17-19]. CAPIRI in the first-line treatment of advanced disease has been associated with response rates of 38%-45% and a time-to-progression (TTP) of about 8 mo with manageable side-effect profiles[20-24], although in some studies an acceptable safety was only achieved by lowering the irinotecan doses[21-23].

Furthermore, the most recent advances in the treatment of mCRC have been possible with the advent of targeted drugs. These include bevacizumab, a recombinant humanized monoclonal antibody to the vascular endothelial growth factor VEGF-A; the predominant member of the VEGF ligand family which is mainly involved in tumor angiogenesis[25]. Bevacizumab was approved by the European Medicines Agency in 2004 for use in combination with any i.v. 5-FU-based therapy for CRC in the first-line setting[26]. Although the trials could be criticized in the choice of a bolus 5-FU/LV regimen which is now considered to be obsolete, a consistent benefit from the addition of bevacizumab has been demonstrated in several studies, including those with capecitabine[27-33].

Whilst still under debate, it appears that combinations of capecitabine, irinotecan and bevacizumab may improve outcome of mCRC patients in trial-experienced hospital centers. However, as many small non-university community-based outpatient clinics are slow to adapt to new combination protocols due to their lack of experience in clinical studies and unfamiliarity with the side effects of these novel combinations, patient data from these out-patient clinics may be quite different to that usually presented from large trials. In the absence of available data on safety and efficacy of CAPIRI +/- bevacizumab (CAPIRI-Bev) in community-based out-patient clinics, we initiated this prospective open-label multicentric trial with a high emphasis placed on such typically community-based out-patient clinics not participating in other clinical mCRC trials[15,16].

MATERIALS AND METHODS

Patient eligibility, study design and treatment

Patients with previously untreated locally advanced or mCRC were eligible for entry into this trial. Histological confirmation of CRC or CRC liver metastases that were not resectable at the time of patient inclusion in the study was required. Additional requirements were an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 (Karnofsky index > 70%) at least one measurable lesion and normal major organ function. Patients were eligible for inclusion, if a previous adjuvant chemotherapy regimen did not include irinotecan and/or bevacizumab. Patients did not have any age restrictions, but life expectancy had to be at least 3 mo.

This was a prospective, open-label multicentric non randomized phase Ⅱ study conducted by Mainz University, with an inclusion period from 2001 to 2006, particularly in nine small community-based German out-patient clinics. Patients were consecutively recruited according to whether they had received either a standard CAPIRI-regimen [capecitabine 1000 mg/m² twice daily (bid), on days 1-14 and irinotecan 200 mg/m² on day 1] or the same regime CAPIRI combined with bevacizumab (CAPIRI-Bev plus bevacizumab 7.5 mg/kg body weight, also on day 1). Patients in both groups received treatment, every 3 wk, in regional out-patient clinics in Germany; treatment choice of bevacizumab was at the discretion of the physician. Treatment continued until first documented tumor progression under therapy. Treatment was halted in cases of clinical progression, severe therapy-associated adverse events and withdrawal of written informed consent. The protocol was approved by the local ethics review boards of all participating institutions. Patient follow up commenced with treatment initiation and ended on 25th July 2008 or with the death of a patient. The resulting median follow-up times for CAPIRI and CAPIRI-Bev were similar, 19.5 and 17.0 mo, respectively.

Participation in the study required patient written informed consent. Patients who had undergone a major surgical procedure within 4 wk before start of treatment were excluded from the trial. Major exclusion criteria included previous treatment with capecitabine, irinotecan and bevacizumab in a palliative setting and participation in another study during treatment. Patients with malignant tumors other than basalioma, successfully treated in situ carcinoma of the cervix or a tumor relapse free period more than 5 years, were excluded from the trial.

Due to the toxicities associated with bevacizumab,

patients with myocardial infarction within 1 year before start of treatment, stroke, thromboembolic events, severe bleeding within 6 mo prior to treatment, hemorrhagic diathesis, unhealing wounds or fractures or proteinuria $\geqslant 1$ in urine sample were excluded. Anticoagulant treatment, thrombocyte-aggregation inhibitors, as well as St. John's wort were prohibited on the date of enrollment to our study.

Statistical analysis

Endpoints: Primary endpoints were response rates (RR) and the toxicity profile; secondary endpoints were progression free survival (PFS) and overall survival (OS) under study treatment.

Response assessment: Tumor response classification was based on the definitions set out in the Response Evaluation Criteria in Solid Tumors (RECIST)[34]. Tumor response was assessed after 12 wk (4 cycles) and all responses were confirmed by further radiological assessment every 12 wk if applicable. The following parameters were calculated: response rates, PFS and OS. The tumor control rate was defined as: complete response (CR) + partial response (PR) + stable disease (SD).

Toxicity measurements: Toxicity was defined as the frequency of hematological and non-hematological, chemotherapy associated adverse events and laboratory changes after 3 mo of treatment. Toxicity of treatment was evaluated at all visits and graded 1 to 4 using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) Version 2.0. For each toxic event the documented maximal NCI-CTC grading throughout treatment was taken into account, to record chemotherapy-associated toxicity in both treatment groups. Particular emphasis was placed on the management of late-onset diarrhea.

Statistical analysis: The study was not set up to significantly compare both groups. However statistical analysis was performed using the full analysis set (intent-to-treat). Statistical analysis including survival analysis according to Kaplan-Meier was performed with the SPSS software package. Survival was measured from the time of diagnosis to the date of death or last follow-up. PFS were calculated from the first day of treatment until progression. Differences in the toxicity profile of both study groups were analyzed by χ^2 test. Value of significance was calculated *via* Fisher's test and $P < 0.05$ was considered significant.

RESULTS

Patient population

A total of 46 patients were enrolled and included in the intent-to-treat analysis of this prospective trial, of whom 17 (37.0%) received treatment with CAPIRI and 29 (63.0%) treatment with CAPIRI-Bev. The patient demographics and baseline characteristics are presented in Table 1. Since patients were not directly randomized but included into the treatment groups at the discretion of the investigators, some clinical parameters (e.g. gender, location of rectum, lymph node metastasis) differed between both groups, but were not statistically different. Patients' age was similar between both patient groups, however there were more female patients in CAPIRI than in the CAPIRI-Bev group (47.1% *vs* 24.1%). The colon was more frequently the primary tumor site in CAPIRI than in the CAPIRI-Bev group (58.8% *vs* 48.2%), which contained fewer patients with sigmoid colon as primary site (5.9% *vs* 20.7%). The liver was the most common metastatic site in both groups (71% and 83%), followed by lymphatic and pulmonary metastases. Previous adjuvant chemotherapy regimen consisted of 5-FU/LV for 6 patients receiving CAPIRI and 4 patients receiving CAPIRI-Bev, and FOLFOX for 2 patients receiving CAPIRI and 4 receiving CAPIRI-Bev.

Table 1 Patient characteristics

	Treatment group	
	CAPIRI	CAPIRI-Bev
N (%)	17 (37%)	29 (63%)
Age (median), years (range)	66 (55-81)	60 (37-80)
Gender, M/F	9/8	22/7
Site of primary tumor, *n* (%)		
Rectum	7 (41.2)	15 (51.7)
Colon	10 (58.8)	14 (48.2)
Site of metastases, *n* (%)[1]		
Hepatic	12 (71)	24 (83)
Pulmonary	6 (35)	11 (38)
Lymphatic and nodal	4 (24)	17 (59)
Skeletal	1 (6)	4 (14)
Peritoneal	1 (6)	5 (17)
Other sites	6 (35)	5 (17)
Performance status (Karnofsky)		
100%	4 (23.5)	17 (58.6)
90%	1 (5.9)	5 (17.2)
85%	1 (5.9)	0 (0)
80%	2 (11.8)	3 (10.3)
70%	4 (23.5)	0 (0)
Adjuvant chemotherapy received	8 (47%)	8 (27.6%)

[1]Patients could have more than one metastatic site.

Treatment compliance

The median number of cycles received was 9 ($n = 17$, CAPIRI) and 8 ($n = 29$, CAPIRI-Bev), and the median duration of therapy was 133 d (> 4 mo) for both groups. Patients in the CAPIRI group received a median dose of 3500 mg capecitabine and 400 mg irinotecan per cycle whereas patients in the CAPIRI-Bev group received 3876 mg capecitabine and 382 mg irinotecan per cycle. At least 1 dose reduction had to be undertaken in 9/29 patients (31%) treated with CAPIRI-Bev and 8/17 patients (47%) treated with CAPIRI. In 55% of the CAPIRI and 53% of the CAPIRI-Bev patients, treatment had to be delayed at least once. The number of hospital admissions during treatment with CAPIRI-Bev was higher than during treatment with CAPIRI (44.8% *vs* 29.4%).

Toxicity

The incidence of hematological and non-hematological

Table 2 Incidence of chemotherapy-related toxicities

	Treatment group			
	CAPIRI (n = 17)		CAPIRI-Bev (n = 29)	
NCI-CTC Grade	Total (1-4)	3-4	Total (1-4)	3-4
Hematologic toxicities, number (%) patients				
Anemia	2 (11.8)	1 (5.9)	4 (13.8)	-
Leukopenia	4 (23.5)	2 (11.8)	6 (20.7)	1 (3.4)
Neutropenia	3 (17.6)	1 (5.9)	5 (17.2)	2 (6.9)
Non-hematologic toxicities, number (%) patients				
Diarrhea	7 (41.2)	5 (29.4)	13 (44.8)	5 (17.2)
Nausea/vomiting	6 (35.3)	-	12 (41.4)	2 (6.9)
Hand-foot syndrome	6 (35.3)	1 (5.9)	9 (31.0)	-
Mucositis	3 (17.3)	2 (11.8)	5 (17.2)	-
Cholinergic syndrome	3 (17.3)	-	2 (6.9)	-
Alopecia[1]	2 (11.8)	-	12 (41.4)	-
Fatigue	2 (11.8)	-	10 (34.5)	-
Anorexia	1 (5.9)	1 (5.9)	2 (6.9)	1 (3.4)
Fever	1 (5.9)	-	4 (13.8)	-
Proteinuria[1]	-	-	7 (24.1)	1 (3.4)
Arterial hypertension	-	-	3 (10.3)	-
Cardiovascular	1 (5.9)	-	1 (3.4)	1 (3.4)
Thromboembolic event	-	-	3 (10.3)	-
GGT rise	1 (5.9)	-	4 (13.8)	4 (13.8)
Hypokalemia	1 (5.9)	1 (5.9)	3 (10.3)	-
Creatinine rise	1 (5.9)	-	1 (3.4)	-

GGT: Gamma-glutamyl transferase; NCI-CTC: National Cancer Institute-Common Toxicity Criteria (version 2), [1]Fisher's test, $P < 0.05$.

toxicities is displayed, by treatment group, in Table 2. Neutropenia and leukopenia were the most frequently reported hematological toxicities, although the number of patients affected by grade 3-4 hematological events was minimal in both groups. Leukopenia was observed in 23.5% *vs* 20.7% (CAPIRI *vs* CAPIRI-Bev). The frequency of neutropenia was equally distributed (17.6% CAPIRI *vs* 17.2% CAPIRI-Bev). Most frequently reported non-hematological toxicities included diarrhea, nausea/vomiting, and hand-foot syndrome (Table 2). The total incidence of diarrhea was similar for CAPIRI and CAPIRI-Bev (41.2% *vs* 44.8%) and grade 3-4 diarrhea was more frequent with CAPIRI (23.5% *vs* 17.2%). Further statistical analysis did not reveal any significant differences between the two groups for non-hematological toxicities. The CAPIRI-Bev group had a significantly higher total incidence of alopecia ($P = 0.049$) and proteinuria ($P = 0.036$), with one Grade 3 proteinuria. Without reaching the level of significance ($P = 0.286$) three cases of arterial hypertension and non-severe thromboembolism were observed for CAPIRI-Bev whereas these events were not observed in the CAPIRI group. All three cases of arterial hypertension were of low NCI-CTC level and were easily managed with oral antihypertensive therapy. One case of minor thromboembolism led to continuation of therapy only without Bev. One cardiovascular event was reported in each group: whereas a stable angina pectoris was reported for CAPIRI, one case of ST-elevated myocardial infarction led to discontinuation of therapy in a patient receiving treatment with CAPIRI-Bev. Thus, the overall grade 3-4 toxicity was reported to be statistically not significant higher in CAPIRI compared to CAPIRI-Bev, 82.4% *vs* 58.6%, respectively.

Table 3 Response rates

	Treatment group	
	CAPIRI (n = 17) number (%) patients	CAPIRI-Bev (n = 29) number (%) patients
Tumor control rate (CR + PR + SD)	13 (70.6)	22 (75.9)
Complete response (CR)	-	-
Partial response (PR)	5 (29.4)	10 (34.5)
Stable disease (SD)	7 (41.2)	12 (41.4)
Progressive disease (PD)	5 (29.4)	6 (20.7)
Not rated	-	1 (3.4)

Table 4 Second-line therapies

	Treatment group	
	CAPIRI (n = 17) number (%) patients	CAPIRI-Bev (n = 29) number (%) patients
Folfiri + Bevacizumab	-	4 (14)
Irinotecan + Cetuximab	-	1 (3)
Capox +/-Bevacizumab	1 (6)	2 (7)
Capox + Cetuximab	-	1 (3)
Folfox +/- Cetuximab	2 (12)	2 (7)
Cetuximab alone	1 (6)	1 (3)
Capiri +/- Cetuximab	-	4 (14)
Capiri + Bevacizumab	1 (6)	-
No second line	10 (59)	14 (48)

Response

Following 3 mo of therapy, response was evaluated in 45 patients. One patient withdrew from CAPIRI-Bev before the 1st assessment. Both groups achieved similar tumor growth control rates (TCR): 70.6% and 75.9% patients treated with CAPIRI or CAPIRI-Bev, respectively. However, there was a difference in response rates, with a not significantly different but higher number of partial responses in the CAPIRI-Bev group (34.5%) compared with the standard CAPIRI group (29.4%) (Table 3). Two patients who achieved a partial response in the CAPIRI-Bev group during the course of treatment were able to undergo a full secondary tumor resection in terms of a curative therapy. No complete responses were observed in either group during follow-up after 3 mo.

Survival

Progression-free survival and overall survival (Figure 1) were in favor of patients receiving CAPIRI-Bev. The median PFS was 11.4 mo (i.e. 342 d) and 12.8 mo (i.e. 385 d) for the CAPIRI or CAPIRI-Bev group, respectively. This difference was not statistically significant (Log Rank, $P = 0.199$). Following second-line protocols in nearly half of all patients (Table 4), the median overall survival was approximately 24 mo in the CAPIRI-Bev group and approximately 15 mo in the CAPIRI group which was not significantly different (Log Rank, $P = 0.53$). The 60 d all

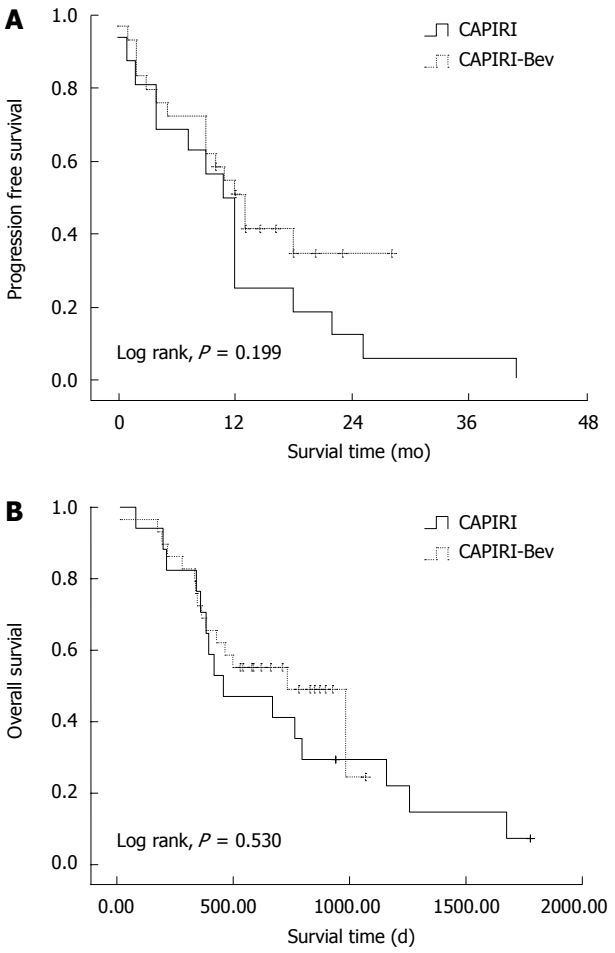

Figure 1 Kaplan Meier survival estimates by treatment group. A: Progression-free survival; B: overall survival. Bev: bevacizumab.

cause mortality was 0% for CAPIRI *vs* 3.4% (1 patient) for CAPIRI-Bev. This patient died 15 d after the first administration of therapy due to unknown cause, (most likely due to progressive disease), with no signs of a cardiovascular or thromboembolic event.

DISCUSSION

This open-label, multicentric, community-based phase Ⅱ trial aimed to prospectively evaluate safety and efficacy of CAPIRI +/- Bev. Most of the 46 patients were recruited by out-patient clinics inexperienced with phase Ⅰ-Ⅲ studies. Thus we propose that these clinics are clearly different from the highly sophisticated centers regularly participating in large registration trials, but however represent the small drug-prescribing centers broadly seen in mCRC patient care for many European and non-European countries. This is also likely to be the reason why the ECOG performance status was not documented in 9 patients. As these primarily conservatively oriented out-patient clinics are relatively slow to adapt to new combination protocols, they also recruited more slowly and enrolled less than one third of their patients into our study (Moehler, personal communications). In addition these patients were those to be treated in a truly palliative setting.

Despite this relatively inexperienced clinical setting, the safety and efficacy of both protocols CAPIRI +/- Bev were remarkably positive. Consistent with other larger trials[29,32,33], a higher RR was obtained with bevacizumab than without (34.5% *vs* 29.4%). The RR in addition to the TCR were almost as high as in a recently presented phase Ⅳ study incorporating FOLFIRI + Bev[35]. Our results also show a higher median PFS and clearly better OS (24 *vs* 15 mo) in patients receiving CAPIRI plus bevacizumab compared to CAPIRI alone, even with less second-line therapies being given (Table 4). Furthermore the increased RR was achieved without a marked increase in toxicity. The incidence of grade 3-4 toxicities was higher in patients not receiving bevacizumab than those receiving it (82.4% *vs* 58.6%, respectively). Notable among these toxicity differences was the higher incidence of Grade 3-4 diarrhea in the CAPIRI group (29.4% *vs* 17.2%), as this was early in recruitment time without clear patient recommendation for the prompt use of loperamide in these relatively inexperienced centers[15,16].

Our efficacy results compare favorably with those obtained with the standard FOLFIRI or FOLFOX regimens[11,12]. Saltz showed in 683 patients, a significant improvement in median PFS and median OS (14.8 *vs* 12.6 mo) and RR were almost doubled; 39% 5-FU/LV + irinotecan *vs* 21% 5-FU/LV, respectively[13]. In the randomized phase Ⅱ study (BICC-C) examining three regimens; FOLFIRI, modified bolus mIFL or CAPIRI, PFS times of 7.8, 6.0 and 5.8 mo and OS of 23.1, 17.6 and 18.9 mo were observed, respectively[36]. After subsequently amending the protocols to include the addition of bevacizumab to the FOLFIRI and mIFL arms, they achieved median PFS times of 11.2 and 8.3 mo and median OS times of 19.2 mo with mIFL + Bev but it was not reached with FOLFIRI + Bev[36].

Furthermore, our results compare well with those from the pivotal phase Ⅲ study with 813 previously untreated patients who received IFL + bevacizumab or placebo[37]. OS for IFL + bev was shown to be 20.3 mo compared to 15.6 mo in the placebo + IFL group. Here, the relatively low median OS for CAPIRI in our study may reflect the fact that our population consisted of patients with poor prognostic factors (5 patients with ECOG PS2) receiving palliative therapy and were not always the typical trial patient population used in large trials. Herein, two large observational studies of the use of chemotherapy plus bevacizumab in broader clinical practice (the BRiTE and BEAT trials) confirm our safety and efficacy results[30,32,33]. The BRiTE community-based registry found that mCRC patients with FOLFIRI + Bev, FOLFOX + Bev, or capecitabine + oxaliplatin (XELOX)-Bev achieved median PFS times of 10.9, 10.3 and 9.0 mo, respectively[30]. The efficacy data from the BEAT community-based trial showed similar median PFS data[32,33].

Thus, in concordance with the early promise of this novel combination in phase Ⅰ/Ⅱ trials[17,18], we postulate that CAPIRI is at least as effective, but is a more convenient alternative to the standard FOLFIRI and FOLFOX regimens. The dose-limiting toxicities were neutropenia

and diarrhea, and dose regimens of capecitabine 1000 mg/m^2 bid for 14 d, and irinotecan of between 250 and 300 mg/m^2 on day 1, once every 3 wk, were proposed. In our study we used capecitabine 1000 mg/m^2 (bid) on days 1-14 and irinotecan 200 mg/m^2 on day 1 (with or without bevacizumab 7.5 mg/kg body weight on day 1), in accordance with Borner's study (2005) with good patient compliance[38]. Furthermore, the safety profile of the recent multicentric phase Ⅱ AIO trial with 247 patients comparing XELOX-Bev with CAPIRI-Bev with a dose of capecitabine 800 mg/m^2, which was 200 mg/m^2 less than used in our trial[39,40] was favorably comparable with the number of adverse events reached in our study. Moreover, the group reported an incidence of Grade 3-4 thromboembolic events of 5% and hypertension of 3%, where these events were not observed in our trial. Similarly, Hochster *et al*[27] reported from both TREE studies a decrease in Grade 3-4 toxicities of approximately 10%-20% for oxaliplatin-based regimens in combination with bevacizumab, which compares well with the decrease of approximately 25% reached by the addition of bevacizumab to CAPIRI in our study.

The overall incidence of grade 3-4 toxicity was higher with CAPIRI than with the CAPIRI-Bev combination: 82.4% *vs* 58.6%, respectively. The grade 3-4 diarrhea, which is the most common dose-limiting toxicity with CAPIRI, was also reduced in those patients receiving CAPIRI-Bev: 29.4% *vs* 17.3%, respectively. This is in clear concordance with recent efficacious and tolerable data on CAPIRI [capecitabine 1000 mg/m^2 (bid), days 1-14; irinotecan 250 mg/m^2 on day 1] in 398 patients, which did not to replicate the toxicity and mortality observed in earlier phase Ⅲ studies incorporating high doses of irinotecan[36,41,42].

In summary, these data are preliminary and should be treated with caution due to the small numbers of patients studied, and because the patients were not randomized to either treatment arm, neither was the study statistically set up to compare treatments. However, taken together, both regimens-CAPIRI alone or with the addition of bevacizumab-were well tolerated and are useful for efficient tumor control in out-patient settings of non-university based out-patient clinics, with the emphasis of patients' recommendations for its possible side effects. Severe gastrointestinal and thromboembolic events seen in other studies[43,44] were rarely observed and never fatal in our study. Thus, many authors concluded that combinations of CAPIRI with both, VEGF or EGFR1 antibodies seemed to be safe and feasible[39].

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COMMENTS

Background

Novel combinations of new chemotherapeutic agents with the increasing number of targeted monoclonal antibodies to tumor expressed antigens, have demonstrated an improvement in tumor response and overall survival in patients with advanced colorectal cancer (CRC) when investigated in the setting of a clinical trial.

Research frontiers

Capecitabine, an oral fluoropyrimidine, irinotecan a topoisomerase inhibitor, and the vascular endothelial growth factor (VEGF) bevacizumab, have demonstrated improved efficacy and tolerable toxicity when compared to with standard therapy following randomized trials in advanced colorectal cancer patients. However few studies have investigated their use in community-based hospital outpatient clinics where many patients with the disease are typically treated.

Innovations and breakthroughs

This is one of the first studies of its kind to investigate capecitabine in combination with irinotecan (CAPIRI) with and without bevacizumab in a community-based hospital out-patients clinic. The data suggest that both treatment regimens demonstrate efficacy and tolerable toxicity in this setting.

Applications

These data are in accordance with the preliminary findings emerging from larger community-based trials which are examining many different treatment combinations in advanced CRC. The data suggest that the improvements in efficacy and safety observed in trials performed in experienced university-based settings in selected patients will be in some cases translated to patients treated in the routine community-based setting, where experience of the use of such new agents is limited, but a substantial proportion of patients with this disease are treated.

Terminology

Capecitabine is an orally administered derivative of 5-fluorouracil (5-FU), sometimes given in preference to intravenously delivered 5-FU due to its ease of administration. It kills tumor cells by preventing DNA synthesis through the inhibition of thymidylate synthase, which is active in proliferating cells. Irinotecan also kills cells by inhibiting the enzyme topoisomerase I which is also involved in DNA synthesis in proliferating cells. Bevacizumab is a monoclonal antibody that inhibits VEGF that is expressed in some CRC aiding the blood supply to tumors; bevacizumab inhibits this process, stopping the tumor cells from growing.

Peer review

This is a non randomized study comparing the efficacy and safety of CAPIRI with and without bevacizumab in the treatment of patients attending community based clinical out-patients clinics. The preliminary results are interesting and may confirm the usefulness of CAPIRI with or without bevacizumab in this clinical setting.

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