Irinotecan and Capecitabine (CAPIRI) Plus Bevacizumab in First-Line Treatment of Metastatic Colorectal Cancer

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Abstract

The purpose of this prospective study was to assess the efficacy and safety of bevacizumab in combination with reduced doses of irinotecan plus capecitabine (CAPIRI regimen), in patients with metastatic colorectal cancer (mCRC), as first-line chemotherapy. A cohort of 120 mCRC consecutive patients was included. The overall response rate was 63.3% (76 patients; 95% confidence interval [CI], 53.97%-71.77%). Median time to progression and overall survival were 15 months (range: 2-49 months; 95% CI: 13.00, 17.00 months) and 22.5 months (range: 4-54 months; 95% CI: 21.00, 27.00 months), respectively. The one year survival rate was 81.5%. CAPIRI-related grade 3/4 adverse events included alopecia (29.2%) and diarrhoea (16.7%), which were manageable. Bevacizumab-related grade 3 hypertension was reported in 2 patients. One patient died due to treatment related adverse event, which was no bevacizumab-related. In conclusion, combination of bevacizumab plus CAPIRI is a feasible treatment which provides a clinical benefit as first-line treatment in chemonaïve patients with mCRC.

Keywords: irinotecan, capecitabine, bevacizumab, colorectal neoplasms, neoplasm metastases

1. Introduction

Approximately 60% of patients with colorectal cancer need chemotherapy to treat their metastatic disease. Chemotherapy was shown to increase the quality of life, time to disease progression (TTP) and overall survival (OS) of patients with metastatic colorectal cancer (mCRC). The introduction in recent years of new chemotherapeutic treatments (e.g. capecitabine, irinotecan, or oxaliplatin) or new regimens with monoclonal antibodies that inhibit specific molecular targets (e.g. bevacizumab, cetuximab, or panitumumab) have substantially improved the efficacy (Colucci et al., 2005; de Gramont. et al., 2000; Hurwitz et al., 2004; Simpson et al., 2003; Tournigand et al., 2004).

Capecitabine offers the advantage of continuous exposure to 5-FU without requiring central venous access (Cassidy et al., 2002; Van Cutsem et al., 2004) and, therefore, it is more convenient to administer, requires less hospitalization and decreases the utilization of medical resources (Payne, 1992). Capecitabine was developed, in combination with either oxaliplatin or irinotecan in a 3 week schedule, instead of 5-FU infusion, as an interesting alternative due to the practicality of the treatment. Moreover, the use of capecitabine instead of 5-FU, either with irinotecan or oxaliplatin, confirmed the activity and efficacy of the drug (Cassidy et al., 2004; Koopman et al., 2007). However, to date no study has shown which regimen (oxaliplatin based or irinotecan-based) is the best in the first and successive lines of treatment. In fact, two studies by Goldberg et al. (2004) and Tournigand et al. (2004) comparing oxaliplatin and irinotecan regimens found no differences in their survival rate and safety profiles. Likewise, studies comparing oxaliplatin and irinotecan regimens in combination with capecitabine were very scarce, as capecitabine doses used in initial comparative studies resulted in an unacceptable level of toxicity (Fuchs et al., 2008). Nevertheless, results from a phase II study by Grothey et al. found minimal differences in survival between capecitabine+oxaliplatin and capecitabine+irinotecan regimens (Schmoll et al., 2006).

In addition, it is important to avoid drugs with cumulative toxicity which can limit their benefits. For oxaliplatin-based regimens, severe peripheral neuropathy led to treatment discontinuation in more than 20% of patients after six months of treatment (Gamelin et al., 2002; Grothey, 2003; Krishnan et al., 2005). Moreover, 5% of the sensitive neuropathies were permanent or persisted for more than two years (de Gramont et al., 2000;

Giacchetti et al., 2000; Hospers et al., 2006). On the other hand, the major adverse events (AEs) associated with irinotecan are diarrhoea and neutropenia, being not cumulative and allowing for continued treatment until disease progression.

New regimens with targeted drugs (e.g. bevacizumab) have shown to prolong the TTP as well. Bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor, combined with fluoropyrimidine based chemotherapy is one of the standard regimens in first line treatment of mCRC and has demonstrated a consistent benefit in several studies (Hurwitz et al., 2004; Macedo et al., 2012).

To gain further information on the efficacy and safety of bevacizumab in combination with reduced doses of capecitabine plus irinotecan (CAPIRI) in a 3-week schedule we decided to prospectively collect the data on this combination from a cohort of mCRC patients attending to our centre. The more favourable cumulative toxicity profile and convenience, made us prefer the low dose CAPIRI treatment in combination with bevacizumab over an oxaliplatin-based regimen. Reduced doses of irinotecan and capecitabine were chosen to increase compliance with the chemotherapeutic regimen while maintaining dose intensity within the activity range for these drugs (Kim et al., 2005). The low dose CAPIRI regimen is extensively used in our unit with acceptable tolerability, based on a previous phase I-II study with irinotecan in second line set conducted in our department (Vieitez et al., 2003). Here, we report the results of this non interventional, single-centre study.

2. Method

2.1 Study Design

The study was performed after obtaining approval from the local Institutional Review Board committee and in accordance with the Declaration of Helsinki, the Good Clinical Practices, and local ethical and legal requirements. The study was performed under standard clinical practice conditions in mCRC patients treated at the University Central Asturias Hospital in Spain. Before inclusion, all patients were fully informed about the study and all gave their written consent.

2.2 Study Population

Patients with histologically confirmed unresectable mCRC, with measurable lesions according to Response Evaluation Criteria in Solid Tumours (RECIST) (Therasse et al., 2000) by computed tomography (CT) scan; aged ≥18 years and Karfnosky performance status (PS) ≥60% were included. Prior chemotherapy for advanced disease was not permitted, but adjuvant or neoadjuvant chemotherapy was allowed providing it was completed at least 12 weeks before inclusion. Prior radiotherapy was permitted if there were measurable lesions outside the radiation field at inclusion. Prior radiotherapy/major surgery must have been completed at least 6 weeks before inclusion. In the absence of symptoms (bleeding, obstruction, and perforation) patients without primary tumour resection or with ascites were eligible.

2.3 Methods

Patients received CAPIRI + bevacizumab treatment, which consisted of a 90 minutes IV infusion of irinotecan 240 mg/m^2 on day 1 plus oral capecitabine 850 mg/m^2 twice daily for 2 weeks plus bevacizumab 7.5 mg/Kg IV on day 1 in a 3-week cycle. Delays or dose reductions for capecitabine (up to 40%) or irinotecan (up to 20%) were permitted according to the tolerance on previous cycle. Chemotherapy was continued until progression, death, unacceptable toxicity or refusal, or lost to follow-up.

The following information was collected from medical records at baseline visit: patients' medical history, Karfnosky PS assessment, and significant findings in blood and urinary tests (including proteinuria and CEA measurement levels). Data from tumour assessments performed were collected from baseline visit and, thereafter, every 2-3 months. The centre's standard clinical practice for tumour assessments includes CT evaluation of the chest, abdomen, and pelvis. Tumour responses were scored according to RECIST v1.0 criteria recommendations (Therasse et al., 2000). The safety was evaluated for all patients receiving at least one dose of the treatment cycle and graded according the National Cancer Institute Common Toxicity criteria (NCI CTCAE) version 2.

Complete liver metastatic resection with curative intention was attempted in patients who were deemed resectable after chemotherapy.

2.4 Statistical Analyses

The primary endpoint of this study was the overall response rate (ORR) assessment; i.e. the percentage of responders (complete response [CR] + partial response [PR]) to treatment with CAPIRI + bevacizumab. The statistical software "Ene-2.0" (Badiella Busquets & Pedromingo, 2010) was used to determine the needed

sample size. Assuming a minimum efficacy of 44.8% (the ORR reported by Hurtwitz et al (Hurwitz et al., 2004) for the IFL + bevacizumab group), a precision of 7.5%, unilateral $\alpha = 0.05$, and $\beta = 0.20$, 119 patients were required. Secondary endpoints included the evaluation of TTP, OS, and the safety profile.

Efficacy analyses included all treated patients. Safety analyses included all patients who received at least one dose of the treatment cycle. TTP was defined as the time from the date of signed informed consent to first documentation of disease progression. TTP was censored at the last tumour assessment or at the date of hepatic surgery for metastatic resection or treatment discontinuation without progression due to AEs. The Kaplan-Meier method was used to calculate the TTP and OS and to estimate the hazard ratio, median values, and 95% confidence interval (CI). A subgroup analysis [including age (< 70, ≥ 70 years); baseline Karnofsky PS (60%, >60%); number of metastatic sites (1, > 1); baseline CEA (value in ng/ml); and KRAS mutation (wild type, mutation)] was performed to identify the effect of patient's baseline characteristics on response rate.

The final analyses were conducted 29 months after the last patient was included.

3. Results

3.1 Patients

Table 1. Baseline patient characteristics

Patient characteristics		Median (range)	n (%)
Age (years)		64 (40-79)	
Gender	Male		88 (73.4)
	Female		32 (26.6)
Karnofsky	60		27 (23)
	70		46 (38)
	80		39 (32)
	90		8 (7)
KRAS gene status	wild-type		64 (53)
	mutated		41 (34)
	unknown		15 (13)
Primary tumour location	Colon (except sigma)		33 (27.5)
	Sigma		42 (35)
	Rectum		45 (37.5)
Baseline metastatic disease location			
	Liver		93 (47.5)
	Only Liver		45 (37)
	Nodes		36 (18)
	Lung		31 (15.5)
	Peritoneum		30 (15)
	Bone		3 (1.5)
	Others		5 (2.5)
CEA baseline value (ng/ml)		33 (0.1-7589)	
LDH baseline value (U/l)		381 (218- 1154)	
Prior treatment	Tumour surgery (resection/derivation)		100 (83.3)
	Colon endoprosthesis		3 (2.5)
	Adjuvant or neoadjuvant chemotherapy		27 (22.5)
	Adjuvant or neoadjuvant radiotherapy		14 (11.7)

Abbreviations: CEA: Carcinoembryonic antigen; LDH: lactate dehydrogenase

The study included, between April 2005 and April 2008, 120 consecutive patients with mCRC treated at the University Central Asturias Hospital in Spain. Table 1 presents patients' baseline characteristics.

At the time of the study analysis (September 2010), 93 patients (77.5%) had died. From the remaining alive patients, 9 patients continued on study treatment and the other 18 patients had discontinued study treatment due to disease progression and were receiving second or further lines of chemotherapy.

3.2 Treatment

The median number of cycles received was 19 cycles/patient (range: 3-42), with a total of 1872 treatment cycles. Median time from informed consent signature was 0 days (range 0-10).

Seventy five patients (62.5%) required an irinotecan dose reduction and 65 patients (54.2%) required a capecitabine dose reduction. However, during the first six cycles, only 10 (8.3%) and 5 (4.2%) patients required an irinotecan or a capecitabine dose reduction, respectively. The most frequent cause of dose reduction/interruption was grade ≥2 diarrhoea for irinotecan and grade ≥2 hand-foot syndrome (HFS) for capecitabine. Other causes of study dose reduction/interruption were neutropenia, mucositis, and thrombocytopenia. The median tolerated irinotecan dose in the first six cycles was 240 mg/m^2 on day 1 every 3 weeks (100% of the foreseen dose intensity [DI]), and was 192 mg/m^2 if considering all cycles (80% of foreseen DI). The median tolerated capecitabine dose in the first six cycles was 850 mg/m^2 twice a day for 14 days every 3 weeks, and was 690 mg/m^2 when all of the cycles were considered (80% of foreseen DI).

A total of 111 patients discontinued study treatment. Reasons for discontinuation were: disease progression in 93 patients, surgical resection of metastases in 10 patients, unacceptable AEs in 7 patients, and death due to arrhythmia which was not related to the study medication in 1 patient.

In total, 81 (86.2%) out of the 93 patients with documented disease progression received subsequent chemotherapy, of which 30, 34, 12, and 5 patients received two, three, four, and five additional lines of treatment, respectively. All these patients received oxaliplatin as second-line chemotherapy, most (n=66; 81.5%) in combination with capecitabine. Third line of treatment consisted of irinotecan in combination with cetuximab or panitumumab in wild-type KRAS patients.

3.3 Efficacy

All the 120 patients were evaluated for response. The ORR was 63.3% (76 patients; 95% CI: 53.97%-71.77%). A CR was observed in 3 patients (2.5%) and a PR was observed in 73 patients (60.8%). Stable disease was achieved in 36 patients (30%) and disease progression was observed in the remaining 8 patients (6.7%) with disease control in 112 (93.3%). Higher response rates were achieved in younger patients (64% vs. 60% for aged <70 and ≥ 70 years, respectively), with better Karnofsky PS (51.8% vs 66.6% for PS ≥ 60% and < 60%, respectively) and with wild-type KRAS status (68.8% with wild-type KRAS vs. 56% with mutant KRAS), although differences between groups were not statistically significant (p>0.05).
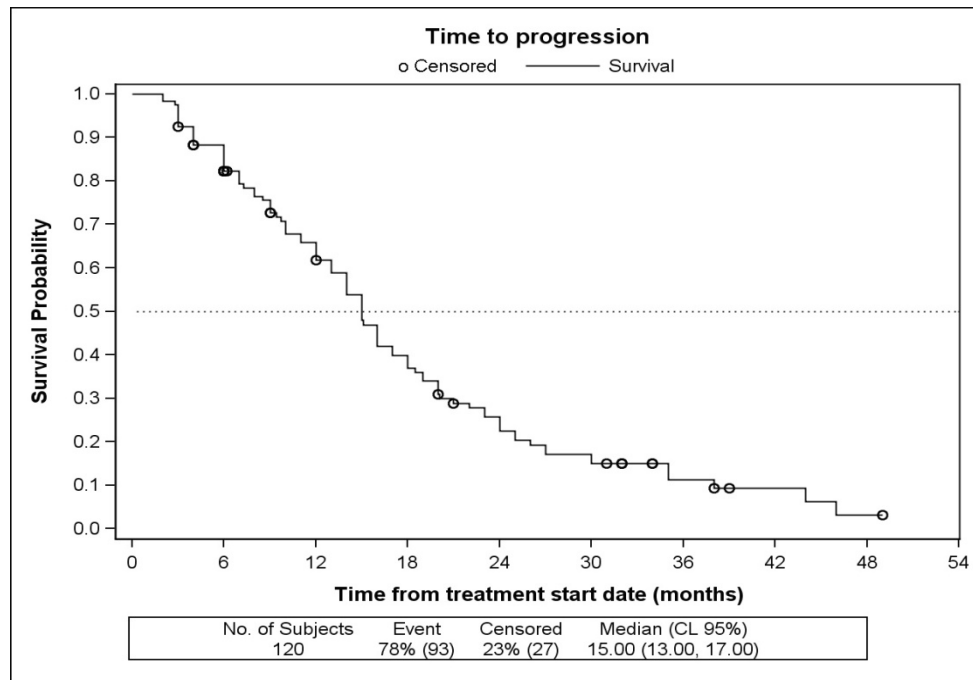
Figure 1. Kaplan-Meier estimates of time to progression

The median TTP was 15 months (range: 2-49 months; 95% CI: 13.00, 17.00 months; Figure 1)
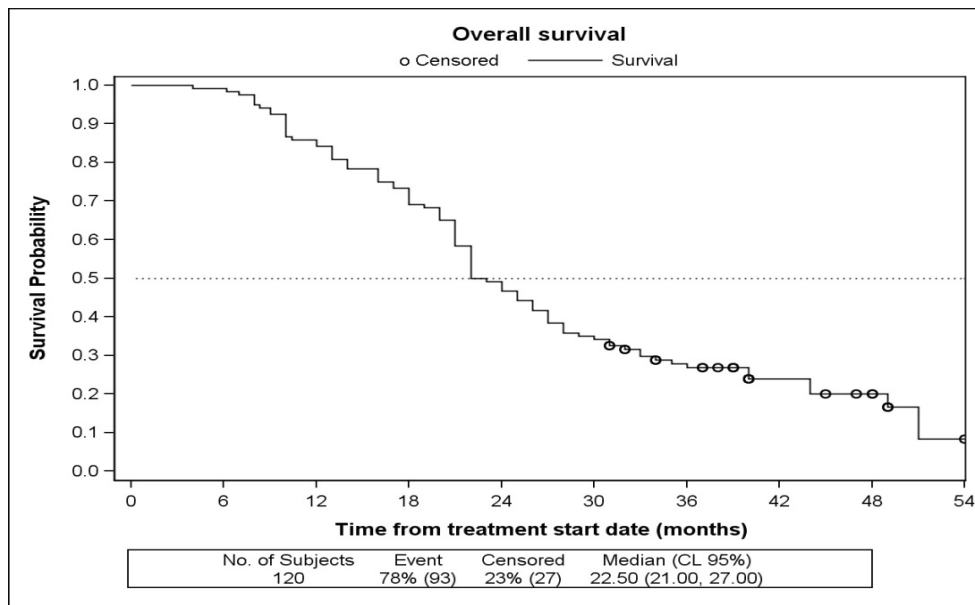
Figure 2. Kaplan-Meier estimates of overall survival

The median OS was 22.5 months (range: 4-54 months; 95% CI: 21.00, 27.00 months). The one year survival rate was 81.5%.

3.4 Liver Metastases Resection

After a median of six cycles of chemotherapy (range: 4-9 cycles), complete liver metastatic resection with curative intention was attempted in 10 (22.2%) out of the 45 patients with unresectable liver metastases at baseline.

The median length of postoperative hospitalization was 10 days (range, 8-29 days). R0 resection was feasible in all 10 patients. Survival rates at one and two year after surgery were 100% and 90%, respectively. Two patients

were disease-free at 38 and 46 months after surgery. Eight patients had recurrence after a median of 18 months (range: 6-43 months) following surgery. Wound healing postoperative complications prolonging hospitalization were reported in 2 patients. Both patients resumed study treatment.

3.5 Safety

Eighty nine patients (74.17%) were reported to have at least one treatment related AE. In total, 508 different treatment-related AEs were documented, being the majority (427 out of 508; 84.1%) with maximum CTC grade ≤2. Table 2 summarizes the incidence of treatment-related AEs.

Table 2. Maximum CAPIRI-bevacizumab related AE per patient according to NCI-CTC grade (n=120)

NCI-CTCAE AEs	Grade 1/2 n (%)	Grade 3/4 n (%)	All grades n (%)
Alopecia	42 (35.0)	35 (29.2)	77 (64.2)
Proteinuria	75 (62.5)	0 (0)	75 (62.5)
Hypertension	72 (60.0)	2 (1.7)	74 (61.7)
Hand-foot syndrome	54 (45.0)	2 (1.7)	56 (46.7)
Hemorrhagic events (bleeding/epistaxis)	51 (42.5)	4 (3.3)	55 (45.8)
Diarrhoea	35 (29.2)	20 (16.7)	55 (45.8)
Neutropenia	32 (26.7)	8 (6.7)	40 (33.3)
Febrile neutropenia	-	3 (2.5)	3 (2.5)
Vomiting	16 (13.3)	2 (1.7)	18 (15.0)
Mucositis	16 (13.3)	0 (0)	16 (13.3)
Acute cholinergic syndrome	16 (13.3)	0 (0)	16 (13.3)
Anaemia	7 (5.8)	0 (0)	7 (5.8)
Thromboembolic events	5 (4.2)	2 (1.7)	7 (5.8)
Thrombocytopenia	3 (2.5)	0 (0)	3 (2.5)
Wound-healing events	2 (1.7)	0 (0)	2 (1.7)
Hyperbilirubinemia	1 (0.8)	0 (0)	1 (0.8)
Febrile neutropenia	-	3 (2.5)	3 (2.5)
Total	427	76	508

Abbreviations: NCI-CTCAE = National Cancer institute Common Toxicity Criteria. Some patients reported more than one AE.

The most common (>20%) treatment-related AEs of any grade were alopecia (n=77, 64.2%); proteinuria (n=75; 62.5%), hypertension (n=74; 61.7%); HFS (n=56, 46.7%), diarrhoea (n=55, 45.8%), hemorrhagic events (n=55; 45.8%), and neutropenia (n=40, 33.3%). A total of 43 patients (35.8%) experienced grade 3/4 AEs, the most common being alopecia (29.2%) and diarrhoea (16.7%). Diarrhoea episodes were resolved after subsequent dose reduction, or treatment cycle delay.

HFS was generally rated as grade 1/2 (96.4%; 54 out of 56); none of the patients had grade ≥2 HFS prior to the fifth cycle. Similarly; hypertension, proteinuria, and epistaxis (n=51; 42.5%) were most of grade 1/2. Grade 3 hypertension was reported in only two (1.7%) patients. Sixty-six out of 74 (89%) patients with previous pharmacologically controlled hypertension presented additional episodes of hypertension, which were overall manageable with antihypertensive medication (angiotensin-converting-enzyme inhibitors, diuretics, or calcium-channel blockers). No arterial thrombotic events were reported in the seven patients with previous venous or arterial history (all of them used prophylaxis anticoagulation doses during the study). No relevant AEs were reported for any of the 21 patients (17.5%) with baseline ascites. There were no bevacizumab related episodes of gastrointestinal perforation or AEs leading to death. One or more cycles of bevacizumab were delayed because of toxicity in 15 patients [hypertension (n=2), thromboembolic events (n=7), hemorrhagic

events (n=4), and wound-healing complications (n=2)] and bevacizumab was reintroduced in 13 of them without further complications. Lung thromboembolism was reported in 2 patients for whom bevacizumab treatment was discontinued as per investigator decision despite the event resolution.

Six patients (5%) discontinued treatment due to treatment-related AEs, 5 of which were considered life threatening: febrile neutropenia leading to death in one patient, lung thromboembolism in two patients and, grade 4 diarrhoea with secondary renal insufficiency and dehydration in two other. The sixth AE leading to discontinuation was a grade 3 hypertension not manageable with oral antihypertensive treatment. One patient was hospitalized due to an opiate intoxication not related to study treatment but for which study treatment was firstly delayed and finally discontinued.

A total of 93 deaths were reported during the study, of which 91 were due to disease progression and two as a result of an AE which was considered treatment-related in one case. This latter was due to febrile neutropenia and occurred during the first 60 days of treatment. None died as a result of progressive disease in the first 90 days.

4. Discussion

The present observational study provides good evidence of the efficacy and good tolerance of the addition of bevacizumab to a reduced dose of CAPIRI in a 3-week schedule for the treatment of patients with mCRC in the first-line setting.

The efficacy results support the adequacy of the CAPIRI low dose regimen (irinotecan dose intensity of 80 mg/m^2 per week) in combination with bevacizumab with an ORR (63.3%), TTP (median 15 months) and OS (median 22.5 months) which are consistent with those reported in other studies with CAPIRI at low doses plus bevacizumab (Ardavanis et al., 2008; Moehler et al., 2009). Moreover, median OS observed in our study was among the range of OS rates (22.5-25.1 months) reported with FOLFIRI (irinotecan dose intensity of 90 mg/m^2 per week) regimen plus bevacizumab (Sobrero et al., 2009) or with bevacizumab plus other routine first-line chemotherapy regimens (Grothey et al., 2008; Van Cutsem et al., 2009).

Although a comparison of results from different phase studies can be only speculative, the efficacy of our schedule is in line with that obtained with oxaliplatin-based regimens combined with capecitabine with/without bevacizumab such as the TREE-2 phase II study (Hochster et al., 2008) or the NO16966 phase III study by Saltz et al. (2008) that showed lower response rates (46% and 49%, respectively) but a similar survival rate (24 and 21.3 months, respectively).

Recent studies on the integration of capecitabine-based regimens with other biologic agents (such as cetuximab) had yielded similar efficacy rates as well. A recent randomized phase II study (AIO KRK 104) in first-line treatment of mCRC found an ORR of 46% for CAPIRI plus cetuximab versus 48% for CAPOX plus cetuximab (Moosmann et al., 2011). The lack of an external control of the radiologic evaluations in our study might partly explain the good results observed in our study. In a recent single-institutional open-label phase II study of irinotecan in combination with capecitabine (XELIRI) plus bevacizumab an ORR of 67.4%, a median PFS of 12.3 months, and a median OS of 23.7 months was found (Garcia-Alfonso et al., 2010).

Different fluorouracil-based treatment regimens with irinotecan have been previously evaluated, and have overall shown a more favourable cumulative toxicity profile and convenience with low doses of CAPIRI (Cartwright et al., 2005; Kim et al., 2005; Park et al., 2004). However, the optimal dosing of CAPIRI has not been fully established. Two international studies (BICC C and EORTC 40015) using high doses of irinotecan (250 mg/m^2) plus capecitabine (2000 mg/m^2 daily for 14 days) given 3-weekly (XELIRI) resulted in an unacceptable level of toxicity (Fuchs et al., 2008; Kohne et al., 2008). Later studies with CAPIRI at lower doses (capecitabine 800-1000 mg/m^2 twice a day for 14 days and irinotecan 200-240 mg/m^2 IV on day 1 every 3 weeks) (Cartwright et al., 2005; Kim et al., 2005; Park et al., 2004), obtained a therapeutic activity similar to that observed with FOLFIRI as well as an acceptable safety profile, particularly when bevacizumab was added to the regimen (Ardavanis et al., 2008; Moehler et al., 2009). In fact, doses as low as 800 mg/m^2 twice a day for capecitabine and 200 mg/m^2 for irinotecan have been proposed as a starting point for future trials based on the regional differences observed in a review of previous studies with capecitabine-irinotecan regimens (Cartwright et al., 2010). Our regimen with little higher doses produces acceptable efficacy with manageable toxicities for most patients. Moreover, lower starting doses of irinotecan and capecitabine can be considered, since in those patients requiring dose reduction of irinotecan (62.5%) and capecitabine (54.2%) the proportion of objective responses was high.

Overall, the safety profile of bevacizumab in combination with irinotecan reported in our study is consistent with that observed in previous clinical studies. (Kozloff et al., 2009; Nalluri et al., 2008; Scappaticci et al., 2007; Scartozzi et al., 2009; Van Cutsem E. et al., 2009). The administration of irinotecan every 3 weeks did not seem to increase the toxicity. In our study a slightly higher incidence of proteinuria, hypertension, and grade 1 bleeding was observed in patients receiving bevacizumab for more than one year. However, a low incidence of grade 2/3 bevacizumab-related AEs and no bevacizumab-related gastrointestinal perforations, grade 4 AEs, or AEs leading to death were seen. Furthermore, bevacizumab did not significantly increase the occurrence of CAPIRI AEs. Moreover, a metaanalysis (Golfinopoulos et al., 2007) of 242 studies in a total of 56,677 patients substantiates the use of irinotecan based regimen plus bevacizumab as first line treatment with a significant improvement in survival when this regimen was used (it was estimated a 8 months prolongation of the absolute survival benefit) which was higher than the benefit obtained with the oxaliplatin based regimen plus bevacizumab as first line treatment (4.7 months of survival prolongation).

In our study, bevacizumab plus CAPIRI allowed potentially curative resection in 10 out of the 45 patients (22.2%) with unresectable hepatic metastases at the time of diagnosis that were deemed resectable after chemotherapy. This percentage of liver resections was similar to other studies (Okines et al., 2009; Van Cutsem et al., 2009; Yoo et al., 2006).

This prospective non-interventional study was performed in one site, which constitutes one important limitation. However, our unselected population based study included 23% patients with Karnofsky 60%, 16.6% patients >70 years and 17.5% patients with ascitis who are usually excluded in clinical trials but which is a representative sample of what is seen in common clinical practice (Hutchins et al., 1999). In addition, the possibility of investigator bias must be always considered due to the nature of the study; non-interventional, single arm, open label and non-randomised. In our study, the lack of a control group for comparison constitutes another study limitation and leaves a room for further improvement.

5. Conclusion

In summary, this study provides evidence of the clinical benefit of bevacizumab, when combined with CAPIRI at low doses, in chemonaïve patients with stage IV colorectal cancer treated in a common clinical practice setting. The use of capecitabine instead of 5-FU infusion can reduce the number of visits to day hospital, while the use of irinotecan instead of oxaliplatin as first-line treatment will possibly avoid the cumulative oxaliplatin doses, thus, reducing neurotoxicity throughout the disease course.

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