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Bevacizumab plus FOLFIRI or FOLFOX in chemotherapy-refractory patients with metastatic colorectal cancer: a retrospective study

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Abstract

Background: The anti-VEGF antibody bevacizumab associated with an irinotecan or oxaliplatin-based chemotherapy was proved to be superior to the chemotherapy alone in first or second line treatment of metastatic colorectal cancer (mCRC). However, it was reported to have no efficacy in 3rd or later-line, alone or with 5FU. The aim of this study was to evaluate the activity of bevacizumab combined with FOLFIRI or FOLFOX in mCRC who have failed prior chemotherapy with fluoropyrimidine plus irinotecan and/or oxaliplatin.

Methods: Thirty one consecutive patients treated between May 2005 and October 2006 were included in this retrospective study. All of them have progressed under a chemotherapy with fluoropyrimidine plus irinotecan and/or oxaliplatin and received bevacizumab (5 mg/kg) in combination with FOLFIRI or simplified FOLFOX4 every 14 days.

Results: Ten patients (32.2%) had an objective response (1 CR, 9 PR) and 12 (38.8%) were stabilized. The response and disease control rates were 45.4% and 100% when bevacizumab was administered in 2nd or 3rd line and 25% and 55% in 4th or later line respectively ($p = 0.024$ and $p = 0.008$). Among the patients who had previously received the same chemotherapy than that associated with bevacizumab ($n = 28$) the overall response rate was 35.7% and 39.3% were stabilized. Median progression free survival (PFS) and overall survival (OS) were of 9.7 and 18.4 months respectively. Except a patient who presented a hypertension associated reversible posterior leukoencephalopathy syndrome, tolerance of bevacizumab was acceptable. A rectal bleeding occurred in one patient, an epistaxis in five. Grade 1/2 hypertension occurred in five patients.

Conclusion: This study suggests that bevacizumab combined with FOLFOX or FOLFIRI may have the possibility to be active in chemorefractory and selected mCRC patients who did not receive it previously.

Background

Colorectal cancer (CRC) is one of the most common human malignancies with more than 300,000 cases both in the United States and in the European Union each year. In the past decade, significant improvements have been performed in response rates, progression-free survival (PFS) and overall survival (OS) [1-4]. Despite these improvements, mainly due to the development of new combinations of standard chemotherapy including 5 fluorouracil, irinotecan and oxaliplatin, nearly all patients with metastatic CRC (mCRC) will die from their disease. Recently, new therapeutic agents targeting molecular events involved in colorectal carcinogenesis have been developed, including bevacizumab, a recombinant humanized monoclonal antibody, which binds to the vascular endothelial growth factor (VEGF) with a high specificity and prevents its interaction with receptors on endothelial cells. VEGF plays a key role in angiogenesis, which is involved in the development of carcinogenesis, tumor growth and malignant dissemination. Therefore, bevacizumab inhibits the activation of VEGF-receptor-mediated signaling pathways and resultant biological effects [5]. This antiangiogenic agent, added to a 5-fluorouracil (5FU) ± irinotecan-based chemotherapy as first-line treatment, has been shown to improve response rates and survival of mCRC patients when compared to the chemotherapy alone [6-8]. An improvement of PFS was also shown in first-line with the addition of bevacizumab to oxaliplatin-based chemotherapy [9]. A randomized phase III study also reported a clinical efficacy of the association of bevacizumab and FOLFOX4 as second-line in mCRC patients previously treated with a fluoropyrimidine and irinotecan, with a significant improvement in response rates, PFS and OS when compared to FOLFOX4 alone [10].

In Europe, bevacizumab was approved by the EMEA (European Medicines Evaluation Agency) in the beginning of 2005 and many CRC patients could not have received it in first or second-line treatment before this date. Moreover, it was reported to have no efficacy in 3rd or later-line, alone or with 5FU [10,11]. The aim of this retrospective study was to evaluate the activity of bevacizumab combined with a chemotherapy with 5FU/LV and irinotecan or oxaliplatin in mCRC who have failed prior chemotherapy with fluoropyrimidine plus irinotecan and/or oxaliplatin.

Methods

Patient characteristics

In this retrospective study, we included all the patients prospectively registered in two centers (Hôpital Ambroise Paré, Boulogne Billancourt and Centre Régional de Lutte contre le Cancer Val d'Aurelle, Montpellier, France) with histologically proven mCRC who had been previously

treated with a fluoropyrimidine (e.g., fluorouracil or capecitabine) plus irinotecan and/or oxaliplatin with no response to treatment (as defined by tumor progression according to the RECIST criteria [12] or unacceptable toxicity) and who then received bevacizumab in combination with FOLFIRI or simplified FOLFOX4 between May 2005 and October 2006. The decision of treatment was always taken during multidisciplinary staff for patients who had not the opportunity to receive bevacizumab at an earlier line of chemotherapy. The usual exclusion criteria were a history of major surgery within 28 days, a thrombotic or bleeding event within 6 months, a hypertension, a clinically significant cardiovascular disease, a hypertension, a therapeutic anticoagulation and the presence of brain metastases. All medical files of the patients were registered prospectively in a computerised database (after national registry council (CNIL) authorization). The following data were collected and analyzed: age and performance status (according to WHO criteria) at the time of the first cycle of bevacizumab, gender, primary tumor site (colon or rectum), number and localization of metastatic sites, previous anticancer drugs received and tumor response to them. This retrospective study was proposed in January 2007 and approved by the local scientific and ethical committee.

Treatment protocols

Patients were treated with bevacizumab given at a dose of 5 mg/kg on day 1 every two weeks, followed by a 2-hour infusion of 400 mg/m² of leucovorin, given simultaneously with a 2-hour infusion of 85 mg/m² of oxaliplatin, followed by a bolus of 400 mg/m² of 5FU and then a 46-hour infusion of 2400 mg/m² of 5FU (simplified FOLFOX4) or the same regimen with a 90 minutes (min) infusion of 180 mg/m² of irinotecan instead of the infusion of oxaliplatin (FOLFIRI) (1 cycle = 14 days). The first infusion of bevacizumab was given over 90 min, the second over 60 min and the following over 30 min when previous infusions were well tolerated.

Tumor evaluation

All the patients must have received at least four cycles of chemotherapy with bevacizumab to be evaluable, but two patients had evidence of a clinical progression before the radiologic evaluation of tumor response and received only three cycles of bevacizumab.

Tumour response was prospectively assessed every four cycles according to RECIST criteria by computerized tomography-scan. Treatment was repeated until the occurrence of disease progression or unacceptable toxicity.

Toxicity was assessed according to the Common Toxicity Criteria version 2.0[13].

Statistical analysis

Fisher's exact test was used to compare response and stabilization rates between groups. The PFS was calculated as the period from the first day of bevacizumab treatment to the date of tumor progression, to death from any cause or to the date of the last follow-up at which data point was censored. The OS time was calculated as the period from the first day of bevacizumab treatment until death of any cause or until the date of the last follow-up, at which data point was censored. Both PFS and OS were estimated by the Kaplan-Meier method and compared using the log-rank test. Analysis was carried out using the STATA software package (College Station, Texas). The level of significance was set at $p = 0.05$.

Results

Patient characteristics

Between May 2005 and October 2006, a total of 31 patients (17 men, 14 women, median age: 60 years) with mCRC resistant to fluoropyrimidine plus irinotecan (96.7%) and/or oxaliplatin (90.3%) received bevacizumab combined with FOLFIRI or FOLFOX4. A total of 373 cycles of bevacizumab combined with chemotherapy were administered, with a median of 12 cycles per patient (range: 3 to 35 cycles).

Patients characteristics are detailed in the table 1. All the patients had a good WHO performance status (≤ 2) at the beginning of bevacizumab therapy except one (WHO PS = 3). The number of metastatic sites were limited to one or two organs in 77% of the cases (24 patients), and metastases were mostly located in the liver (84%) or lung (42%). Twenty seven patients (87%) had previously received fluoropyrimidine, irinotecan and oxaliplatin and 19 (61%) had received cetuximab. In 19 out of 20 patients who received bevacizumab in 4th-line or further (L4+), cetuximab was previously used and failed, five patients previously received a monotherapy of fluoropyrimidine (capecitabine ou 5FU), four patients were treated by the association of capecitabine and mitomycin-C and five by hepatic arterial infusion of oxaliplatin and intravenous LV5FU2. Bevacizumab was combined with FOLFIRI in 19 cases and with FOLFOX in 12 cases and was administered equally as third, fourth and fifth or later-line (32% in each group). One patient was treated in second line but he was progressive under a combination of 5FU, irinotecan and oxaliplatin (FOLFIRINOX regimen).

Response rates

The overall response rate was 32.2% (table 2). One patient (3.2%) had a complete response and 9 (29%) a partial response. Among them, one patient could have a resection of liver metastases after a partial response to FOLFIRI plus bevacizumab and was alive without relapse at the last follow-up. Twelve patients (38.8%) had a stable

Table 1: Patients characteristics

Characteristics	
Sex: Male/Female	17/14
Age (years)	
Median	60
Range	24-81
WHO Performance status, n(%)	
0	10 (32)
1	16 (52)
2	4 (13)
3	1 (3)
Primary tumor location, n (%)	
Colon	23
Rectum	8
Metastatic sites, n (%)	
Liver	26 (84)
Lung	13 (42)
Peritoneum	5 (16)
Others	12 (39)
Number of metastatic sites, n (%)	
1	15 (48)
2	10 (32)
≥ 3	7 (23)
Chemotherapy associated with bevacizumab, n (%)	
FOLFIRI	19 (61)
FOLFOX4	12 (39)
Line number of bevacizumab, n (%)	
2 nd line	1 (3.25)
3 rd line	10 (32.25)
4 th line	10 (32.25)
5 th or later-line	10 (32.25)
Previous chemotherapy	
Fluoropyrimidine + irinotecan + oxaliplatin	27
Fluoropyrimidine + irinotecan	3
Fluoropyrimidine + oxaliplatin	1
Cetuximab	19

disease, with a disease control rate of 71%. The response rate was 45.4% when bevacizumab was administered in 2nd and 3rd-line (L2-L3) and 25% when it was administered in 4th-line and further (L4+) respectively (table 2; $p = 0.024$). It was 36.9% when bevacizumab was associated with FOLFIRI and 25% when associated with FOLFOX ($p = 0.6$). The disease control rate was 100% when bevacizumab was administered in L2-L3 and 55% when it was administered in L4+ respectively (table 2; $p = 0.008$). Most of the patients ($n = 28$; 90%) had previously received the same chemotherapy (FOLFOX or FOLFIRI) than that associated with bevacizumab. Among these patients, the overall response rate was 35.7% and 39.3% were stabilized (table 2).

Survival

With a median follow-up period of 35.9 months (range: 33 to 37.4 months) from the beginning of bevacizumab administration, the median PFS was 9.7 months (95% confidence interval (CI): 6.6-13.6) (figure 1) and the

Table 2: Overall response rates

	Patients (n)	CR (%)	PR (%)	SD (%)	PD (%)
Overall	31	1 (3.2)	9 (29)	12 (38.8)	9 (29)
2 nd and 3 rd line	11	0 (0)	5 (45.5)	6 (55.5)	0 (0)
4 th and later line	20	1 (5)	4 (20)	6 (30)	9 (45)
FOLFIRI	19	1 (5.3)	6 (31.6)	8 (42.1)	4 (21)
FOLFOX	12	0 (0)	3 (25)	4 (33.3)	5 (41.7)
Same CT previously used					
Yes	29	1 (3.5)	9 (31)	11 (37.9)	8 (27.6)
No	2*	0 (0)	0 (0)	1 (50)	1 (50)

CR; complete response, CT; chemotherapy; PR; partial response, SD; stable disease, PD; progression disease. * no previous treatment by FOLFOX in two patients treated by bevacizumab + FOLFOX

median OS was 18.4 months (95%CI: 13.6- not reached) (figure 2).

Toxicity

There was no toxic death. The incidence of haematological and non-hematological toxicity is summarized in Table 3. A grade 3/4 toxic event occurred in 19,3% of patients. A cytotoxic dose reduction or interruption and a delay in chemotherapy cycles was required in 51% and 13% of patients respectively. As concerns bevacizumab-induced toxicity, only one interruption was required in a patient who presented a reversible posterior leukoencephalopathy syndrome attributed to bevacizumab therapy because of associated hypertension. This syndrome was revealed by a generalized tonic-clonic seizure and diagnosed on magnetic resonance imaging of the brain [14]. Except this severe adverse event, tolerance of bevacizumab was acceptable, without bowel perforation, thromboembolism event, severe bleeding or hypertension. A minimal rectal bleeding occurred in one patient

and a grade 1/2 hypertension in five patients, which was easily manageable by an antihypertensive treatment. An epistaxis also occurred in five patients.

Discussion

This study reports an activity of bevacizumab at the dose of 5 mg/kg combined with FOLFOX or FOLFIRI regimen in patients who have failed prior chemotherapy with fluoropyrimidine, irinotecan and/or oxaliplatin. Indeed, 32% of the patients could achieved an objective response and one patient could secondary have a curative resection of its liver metastases. The disease control rate was superior to 70%. The addition of bevacizumab to FOLFIRI or FOLFOX was also associated with a PFS and a OS of 9.7 months and 18.4 months respectively. These response and survival rates are higher than those reported by Gian-tonio et al. with the combination of FOLFOX plus bevacizumab in second line treatment in patients previously treated by fluoropyrimidine and irinotecan, but this might be certainly explained by the small size and the ret-

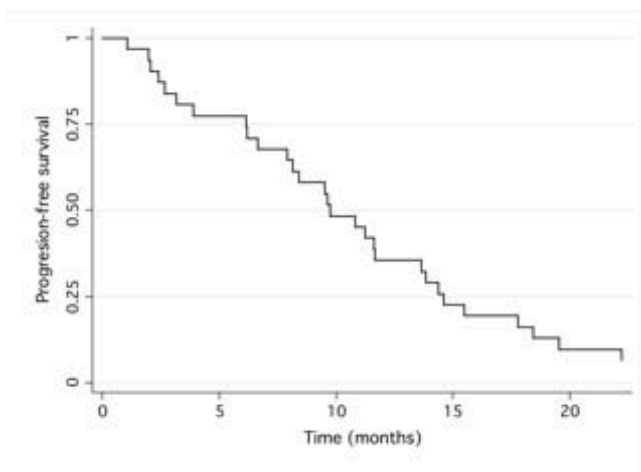


Figure 1
This figure displays a graph showing 'Progression free survival'.

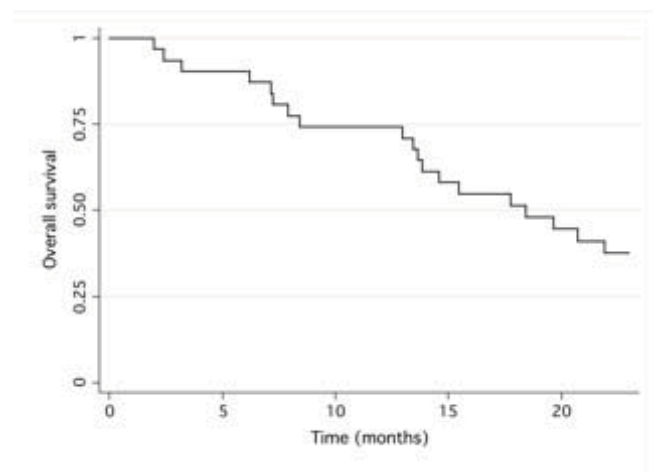


Figure 2
This figure displays a graph demonstrating 'Overall survival'.

Table 3: Chemotherapy-induced toxicity (NCI-CTC version 2.0)

	Grade 1, n	Grade 2, n	Grade 3, n	Grade 4, n
Neutropenia	0	3	1	0
Thrombocytopenia	2	1	0	0
Anemia	0	2	1	0
Diarrhea	10	4	1	0
Nausea-vomiting	10	9	2	0
Alopecia	3	0	0	0
Hand-foot syndrome	0	1	0	0
mucositis	6	0	2	0
Neurotoxicity	3	3	4	0
Asthenia	9	7	3	0
Allergic reaction	0	1	0	0
Maximum/patient (%)	4 (12,9)	15 (48,4)	6 (19,3)	0 (0)

NCI-CTC: National Cancer Institute Common Toxicity Criteria.

respective nature of our study. Furthermore, patients who received bevacizumab during the period of the study were highly selected because bevacizumab was not registered in this setting but only in first line treatment. For these reasons, our results have to be taken with caution. However, they are nonetheless interesting in third-line treatment where few molecules have been shown to be effective. In patients pretreated with fluoropyrimidine, irinotecan and/or oxaliplatin, several studies have reported poor response and survival rates with standard chemotherapy such as the association of mitomycin C and capecitabine [15-18]. The antibodies against the Epidermal Growth Factor Receptor (EGFR) are the only therapy to have shown their efficacy in chemorefractory CRC patients. Cetuximab was the first to show a significant response rate in association with irinotecan in irinotecan-refractory mCRC in the phase II BOND study, in which PFS and OS were of 4.1 and 8.6 months respectively [19]. The superiority of cetuximab monotherapy over best supportive care (BSC) in terms of survival was demonstrated more recently [20]. The fully human anti-EGFR antibody panitumumab was also associated with a longer PFS when compared to BSC in a recent randomized phase III trial [21]. However, it is now clearly demonstrated that patients with a tumor *KRAS* mutation are resistant to anti-EGFR antibodies and do not benefit from this targeted therapy [22-26]. Bevacizumab should therefore be considered for these patients after failure of conventional chemotherapy. In our study, 61% of the patients had previously received cetuximab and were so resistant to all potentially efficient therapies approved in the treatment of mCRC.

In patients who were previously treated with the same chemotherapy regimen (90% of all patients included), the addition of bevacizumab to this regimen allowed a response rate of 35.7% and a stabilization of 39.3%, which suggests that the antiangiogenic therapy may circumvent resistance to conventional chemotherapy by

allowing a more efficient delivery of chemotherapeutic agents. Tumor vasculature is structurally and functionally abnormal, which results in a heterogeneity in tumor blood flow with interstitial hypertension, hypoxia and acidosis [27]. Hypoxia could therefore render tumor cells resistant to several cytotoxic drugs by interfering with the penetration of these drugs throughout the tumor. The concept of "normalization" of tumor vasculature induced by bevacizumab, developed by Jain [28] who demonstrated with some colleagues this effect of VEGF blockade in rectal carcinoma [29], may therefore explain the circumvention of resistance to conventional therapies observed in our study. This phenomenon does not seem to be observed with the combination of an anti-EGFR antibody with bevacizumab considering the disappointing results of two recent randomized studies in which the addition of cetuximab or panitumumab to bevacizumab in combination with a conventional chemotherapy was not associated with any benefit but on the contrary perhaps with a deleterious effect [30,31], which remains to be elucidated.

A first randomized phase II trial of bevacizumab plus bolus 5FU/LV compared to 5FU/LV alone in untreated mCRC suggested an improvement of response rate, PFS and OS with the combined treatment [7]. Then, the large randomized phase III study reported by Hurwitz et al. [6] demonstrated that the addition of bevacizumab to irinotecan and bolus 5FU/LV (IFL regimen) in first-line treatment was associated with a significant prolongation of PFS (6.2 months versus 10.6 months) and OS (15.6 months versus 20.3 months), as a better response rate (34.8% versus 44.8%). The results of that pivotal study led to the registration of bevacizumab in the first-line setting in the United States and in Europe. The association of bevacizumab to 5FU/LV was also shown to provide a statistically significant and clinically relevant benefit to patients with previously untreated mCRC [6-8,32]. More recent

studies showed that bevacizumab with FOLFIRI or FOLFOX4 regimen was superior to the chemotherapy alone in this setting [9,33]. In second-line, the ECOG E3200 phase III trial showed that bevacizumab improved response rate, PFS and OS when added to the FOLFOX4 regimen in patients pre-treated with a fluoropyrimidine and irinotecan [10]. Bevacizumab in combination with 5FU/LV plus irinotecan or oxaliplatin is therefore proved to be beneficial in first and 2nd-line setting. In the absence of cross-over after progression in the chemotherapy arm of the studies evaluating the addition of bevacizumab to a combined chemotherapy [6,10], the effect of the antiangiogenic agent associated with a bichemotherapy after the 2nd-line of treatment is not known. However, it was associated with a poor response rate (1%) in combination with a bolus regimen of 5FU/LV in chemotherapy-refractory mCRC [11]. In this large multicenter phase II study, PFS and OS were 3.7 months and 9.1 months respectively. This result, adding to the lack of efficacy of bevacizumab in monotherapy [10] led us to test it in this setting in combination with the more active FOLFOX4 or FOLFIRI regimens. Bevacizumab was administered at the dose of 5 mg/kg every 2 weeks as it was reported in first-line studies with 5FU/LV/irinotecan or oxaliplatin [6,9,33] and since the 10 mg/kg dose was not previously shown to be superior [7].

Our results are consistent with those of a recent small study conducted in 14 mCRC patients that progressed after oxaliplatin and irinotecan and for whom bevacizumab plus infusional 5FU/LV and irinotecan allowed a 28.5% response rate with 57% of stabilized patients [34]. Median PFS was 3.9 months and OS was 10.9 months.

In our study, bevacizumab was well tolerated, with only one interruption due to a reversible posterior leukoencephalopathy syndrome associated with hypertension [14]. The other adverse events were easily manageable. As concerns chemotherapy-induced toxicity, it was relatively low because most of the patients previously received the same regimen as that associated with bevacizumab. Therefore required dose modifications were already performed before starting bevacizumab therapy

Conclusion

Taking together, these results from retrospective data suggest that bevacizumab combined with FOLFOX or FOLFIRI may have the possibility to be active in chemorefractory and selected mCRC patients who did not receive it previously.

Competing interests

AL and MY: received honoraria from Roche France

PR: received research grant from Roche France

Authors' contributions

AL, JBB, ES, CBG collected the clinical data. AL, ES, EM, EA, CL, JBB, FP, JNV, MY and PR treated and followed the patients included in the study. PR, EM, MY and AL were involved in the conception of the study. EM performed the statistical analysis. AL wrote the manuscript. ES, EM, PR and MY were involved in the interpretation of data and critically revised the manuscript. All the authors read and approved the final manuscript.

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