Preoperative Chemotherapy Plus Bevacizumab and Morbidity after Resection of Colorectal Cancer Liver Metastases

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Abstract: *Aims and background*: The addition of bevacizumab to preoperative chemotherapy is a common therapeutic practice in patients with colorectal liver metastases. The aim of the present study was to assess the effect of bevacizumab on postoperative complications after liver resection.

Methods: A retrospective analysis was performed including patients who underwent liver resection for colorectal liver metastases after receiving chemotherapy with or without bevacizumab in two hospitals. Univariate logistic regression models were used to identify predictors of postoperative morbidity in both groups of patients.

Results: A total of 76 patients were analyzed: 22 patients did not receive preoperative chemotherapy (control group), 21 patients received preoperative chemotherapy alone and 33 patients received preoperative chemotherapy in combination with bevacizumab. The median number of chemotherapy cycles received was 4 (range, 1-23) for the chemotherapy group and 7 (range, 2-36) for the chemotherapy plus bevacizumab group Morbidity rate was similar in the three groups of patients considered: 54.5 %, 47.6% and 39.4, respectively. The most common complications were infections and wound complications. The number of preoperative chemotherapy cycles received was the only clinical variable that was significantly correlated with postoperative comorbidity.

Conclusions: Our results support the evidence that the addition of bevacizumab to preoperative chemotherapy does not increase the risk of complications following surgery of colorectal liver metastases.

Keywords: Colorectal liver metastases, bevacizumab, postoperative complications, preoperative chemotherapy, surgery complications.

INTRODUCTION

Colorectal cancer is the most common gastrointestinal malignancy and the second cause of cancer death in Europe [1]. The liver is the most usual site of organ metastases from colorectal cancer. Treatment strategies in patients with colorectal liver metastases are tailored according to resectability status [2].

Complete surgical resection of colorectal liver metastases is potentially curative and provides clear survival benefits. Therefore, surgery is considered as the standard treatment approach for patients with resectable, liver-only metastases [3,4]. Since definition of metastases resectability varies considerably and may diverge between surgeons and clinics, sometimes is difficult to determine which patients are amenable to surgical resection. Therefore, the collaborative work of multidisciplinary teams is essential for coordinating the care of patients with colorectal liver metastases [5,6].

Despite the clear benefits of surgery, only 15-20% of patients with colorectal liver metastases are initially candidates for surgery [7,8]. In patients unable to be resected initially, metastases shrinkage with downsizing preoperative chemotherapy could allow undergo subsequent resection. Nowadays, this strategy is included in available clinical guidelines [4,6]. The combination of perioperative chemotherapy and surgery is also a common therapeutic option in patients with initially resectable metastases. The results of the EORTC 40983 trial support this practice [9]. The addition of targeted therapies to combination chemotherapy for metastatic colorectal cancer resulted in improved outcomes. Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEFG), is usually added to cytotoxic chemotherapy in patients with advanced disease [10-12].

Peri- and postoperative complications are a major concern associated with preoperative chemotherapy. While oxaliplatin-based regimens are related to a

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higher risk of hepatic vascular lesions, irinotecan-based regimens are associated with an increased risk of steatosis and steatohepatitis [13-16]. The addition of bevacizumab to preoperative chemotherapy adds further concerns about per- and postoperative morbidity due to the effect that a VEFG inhibitor may have on liver regeneration and wound healing. In order to prevent peri- and postoperative complications, bevacizumab should be administered with some precautions. Thus, it is recommended a timely discontinuation (six weeks) of bevacizumab prior to surgery [5].

The aim of the present study was to assess the effect of bevacizumab on postoperative complications after liver resection for colorectal liver metastases and to identify potential demographic and clinical factors that may be associated with a higher risk of postoperative morbidity.

MATERIALS AND METHODS

Design

We performed a retrospective cohort study of all consecutive patients who underwent liver resection for colorectal liver metastases after receiving chemotherapy with bevacizumab in two hospitals (Hospital General Universitario and Hospital La Fe, Valencia, Spain) between January 2005 and June 2010. The study was approved by the Ethics Committee of Clinical Research of both hospitals and was conducted according to the Declaration of Helsinki for studies in humans.

All patients who underwent hepatic surgery for colorectal liver metastases after receiving chemotherapy with bevacizumab (CTB group) were eligible for inclusion in the present analysis. A multidisciplinary team of surgeons and oncologists coordinated management of all cases and decided on the strategy of preoperative management. Other two groups of contemporary patients were also included in the study in order to compare the postoperative morbidity: patients undergoing surgery after receiving chemotherapy without bevacizumab (CT group) and patients undergoing surgery without preoperative chemotherapy (control group).

The primary endpoint of the study was the occurrence of postoperative complications. Additionally, liver resection outcomes, relapse-free survival and overall survival after liver resection were compared between groups CTB and CT for drescriptive purposes.

All patient data were retrospectively collected form clinical charts and included demographic variables, comorbidities, disease status at diagnosis, information regarding preoperative treatment received, adverse events related to bevacizumab treatment (bleeding, hypertension, thromboembolic events and perforations) graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0., liver resection details, postoperative complications reported and survival status data. The following postoperative complications occurred within the 90 days after the resection were collected: wound complications, bleeding, thromboembolic complications, hepatic complications and other complications. Hepatic insufficiency was defined by an increased international normalized ratio (INR) together with hyperbilirubinemia on or after postoperative day 5 [17].

Descriptive statistics were obtained for all variables. Numerical variables were summarized as median and range. For categorical variables, absolute and relative frequencies were calculated. One-way ANOVA or Kruskal-Wallis tests were used to compare continuous variables, while chi-square tests or Fisher's exact tests were applied for categorical data.

Univariate logistic regression models were used to identify predictors of postoperative morbidity in the CT and CTB groups. Odds ratios (OR) with 95% confidence interval (CI) of the risk of preoperative complications were calculated. The following variables were considered in the univariate analyses: age, sex, concomitant extrahepatic disease, preoperative chemotherapy received (oxaliplatin- or irinotecan-based chemotherapy), preoperative treatment duration, number of preoperative chemotherapy cycles, metastases size, number of metastases and time from the discontinuation of bevacizumab to surgery. Time-to-event data were analyzed using the Kaplan-Meier method. A *p*-value of less than 0.05 was considered statistically significant. Data analysis was performed using the Statistical Analysis System (SAS 9.1).

RESULTS

A total of 76 patients were included in the present retrospective analysis: 22 patients did not receive preoperative chemotherapy (control group), 21 patients received preoperative chemotherapy alone (CT group)

and 33 patients received preoperative chemotherapy in combination with bevacizumab (CTB group). Demographic and clinical characteristics at baseline are shown in Table **1**. There were no significant differences between groups CT and CTB. It is noteworthy that pre-hepatectomy carcinoembryonic antigen (CEA) levels were significantly higher in the CT group (p= 0.004).

Patients included in the control group were significantly older than in the other two groups, and presented a lower proportion of high-stage tumours and a higher proportion of metachronous liver metastases.

As was expected, all metastases in the control group were considered initially resectable or potentially resectable. Four (19.1%) patients in the CT group and 8 (24.2%) patients in the CTB group presented with initially unresectable metastases. Therefore, preoperative chemotherapy allowed these patients became resectable after their metastases had been downsized by chemotherapy (alone or in combination with bevacizumab).

The median number of chemotherapy cycles was 4 (range, 1-23) for the CT group and 7 (range, 2-36) for the CTB group (Table **2**). Most patients received oxaliplatin-based chemotherapy regimens: 81% and

Table 1: Demographic and Clinical Data at Diagnosis According to Preoperative Treatment Received

	Control group N= 22	Chemotherapy N= 21	Chemotherapy plus bevacizumab N= 33	*p* value
Age (years), median (range)	67.0 (47.0-82.0)	61.0 (44.0-79.0)	59.0 (44.0-73.0)	0.002[a]
Females, n (%)	6 (27.3)	8 (38.1)	5 (15.2)	0.158[b]
Presence of comorbidities, n (%)	12 (54.5)	12 (57.1)	17 (51.5)	0.914[b]
Hypertension	7 (31.8)	6 (28.6)	13 (39.4)	
Cardiovascular	2 (9.1)	2 (9.5)	4 (12.1)	
Diabetes	2 (9.1)	2 (9.5)	3 (9.1)	
Pulmonary	2 (9.1)	1 (4.8)	1 (3.0)	
Renal	1 (4.6)	0 (0.0)	1 (3.0)	
Hepatic	0 (0.0)	1 (4.8)	1 (3.0)	
Cancer stage at diagnosis, n (%)				0.018[c]
I	2 (9.1)	0 (0.0)	1 (3.0)	
II	7 (31.8)	0 (0.0)	1 (3.0)	
III	4 (18.2)	0 (0.0)	5 (15.2)	
IV	9 (40.9)	21 (100.0)	26 (78.8)	
CEA (ng/ml), median (range)	3.0 (0.0-33)	38.0 (1.6-205.0)	4.4 (0.0-440.0)	0.004 [d]
Location of primary tumour, n (%)				0.257[b]
Colon	18 (81.8)	13 (61.9)	26 (78.8)	
Rectum	4 (18.2)	8 (38.1)	7 (21.2)	
Liver metastases, n (%)				< 0.001[b]
Synchronous	9 (40.9)	21 (100.0)	27 (81.8)	
Metachronous	13 (59.1)	0 (0.0)	6 (18.2)	
Resectability of liver metastases, n (%)				< 0.001[c]
Resectable metastases	21 (95.5)	8 (38.1)	16 (48.5)	
Potentially resectable metastases	1 (4.6)	9 (42.9)	9 (27.3)	
Unresectable metastases	0 (0.0)	4 (19.1)	8 (24.2)	
Concomitant extrahepatic disease, n (%)	4 (18.2)	1 (4.8)	4 (12.1)	0.445[b]

Abbreviations: CEA = carcinoembryonic antigen.
[a]ANOVA test.
[b]Chi-square test.
[c]Fisher exact test.
[d]Kruskal-Wallis test.

Table 2: Data on Preoperative Treatment

	Chemotherapy N= 21	Chemotherapy plus bevacizumab N= 33
Total number of preoperative chemotherapy cycles, median (range)	4.0 (1.0-23.0)	7.0 (2.0-36.0)
Type of preoperative chemotherapy, n (%)		
Oxaliplatin	17 (81.0)	25 (75.8)
Irinotecan	4 (19.0)	7 (21.2)
Capecitabine	0 (0.0)	1 (3.0)
Clinical response, n (%)*		
Complete response	1 (4.8)	2 (6.1)
Partial response	20 (95.2)	25 (75.8)
Stable disease	0 (0.0)	5 (15.2)
Progression	0 (0.0)	0 (0.0)

*Note that this clinical response rate is calculated in patients who underwent hepatic surgery of colorectal liver metastases.

75.8% in the CT group and in the CTB group, respectively. Three patients in the CTB group received a second-line of neoadjuvant chemotherapy; all of them had received oxaliplatin-based chemotherapy plus bevacizumab as first-line treatment. The second-line treatment was given in order to improve the response to the therapy.

As for adverse events related to bevacizumab treatment, 5 (15.2%) presented hypertension, 3 (9.0%) bleeding and 2 (6.1%) thromboembolic events. No patient presented with perforations associated with bevacizumab treatment.

Most patients in both groups presented a partial response to preoperative treatment. Two patients in the bevacizumab group presented a complete clinical response to neoadjuvant chemotherapy (Table **2**). The last dose of bevacizumab in the chemotherapy plus bevacizumab group was received in a median interval of 7.3 weeks (range, 3.6-42.4 weeks) before liver resection.

Details of liver resection are displayed in Table **3**. The proportion of patients who underwent major resection was similar in the two groups: 47.6% (n= 10) in the CT group and 36.4% (n= 12) in the CTB group. Most patients in both groups presented a complete resection. However, a higher proportion of patients in the CT group achieved a complete resection of their metastases: 95.2% compared with 72.7% in the CTB group.

Morbidity rate was similar in the three groups of patients considered: 54.5 % in the control group, 47.6% in the CT group and 39.4% in the CTB group (Table **4**). There were no deaths due to postoperative complications in any of the groups considered.

Table 3: Liver Resection Characteristics

	Chemotherapy N= 21	Chemotherapy plus bevacizumab N= 33
Type of resection, n (%)		
Major resection	10 (47.6)	12 (36.4)
Minor resection	11 (52.4)	21 (63.6)
Number of hepatic metastases at liver resection, n (%)		
≤ 3 metastases	17 (81.0)	26 (78.8)
> 3 metastases	4 (19.0)	7 (21.2)
Resection margins, n (%)		
Complete resection	20 (95.2)	24 (72.7)
Positive margins	1 (4.8)	9 (27.3)

Table 4: Peri- and Postoperative Complications

	Control group N= 22	Chemotherapy N= 21	Chemotherapy plus bevacizumab N= 33	*p* value
Morbidity, n (%)	12 (54.5)	10 (47.6)	13 (39.4)	0.536[a]
Mortality, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1.000[b]
Perioperative blood transfusion, n (%)	4 (18.2)	5 (23.8)	8 (24.2)	0.883[b]
Hepatic complications, n (%)	0 (0.0)	5 (23.8)	6 (18.2)	0.050[b]
Hepatic insufficiency	0 (0.0)	2 (9.5)	3 (9.1)	
Biliary fistula	0 (0.0)	3 (14.3)	2 (6.1)	
Others	0 (0.0)	0 (0.0)	1 (3.0)	
Wound complications, n (%)	5 (22.7)	3 (14.3)	9 (23.3)	0.569[b]
Bleeding/thromboembolic complication, n (%)	1 (4.6)	2 (9.5)	2 (6.1)	0.725[b]
Respiratory insufficiency, n (%)	0 (0.0)	0 (0.0)	2 (6.1)	0.502[b]
Coagulopathy, n (%)	1 (4.6)	0 (0.0)	1 (3.0)	1.000 [b]
Intra-abdominal abscess, n (%)	0 (0.0)	0 (0.0)	1 (3.0)	1.000[b]
Renal failure	1 (4.6)	0 (0.0)	1 (3.0)	1.000[b]
Infection	4 (18.2)	4 (19.0)	2 (6.1)	0.265[b]
Abdominal pain of unknown aetiology	0 (0.0)	2 (9.5)	0 (0.0)	0.074[b]

[a]Chi-square test.
[b]Fisher exact test.

The proportion of patients that needed blood transfusions was similar in the three groups (p= 0.883). The most common postoperative complications were those related with the wound; there were no statistically significant differences between the three groups in the frequency of wound complications (p= 0.569). While no patients in the control group presented hepatic complications, 5 patients in the CT group and 6 in the CTB group presented a hepatic complication (see Table **4**). The proportion of other postoperative complications was similar in the three groups of patients (p> 0.05).

Six (27.3%) patients in the control group, 4 (19.0%) in the CT group and 6 (18.2%) in the CTB group were readmitted due to postoperative complications.

The number of preoperative chemotherapy cycles received was the only clinical variables that was correlated with postoperative comorbidity in the

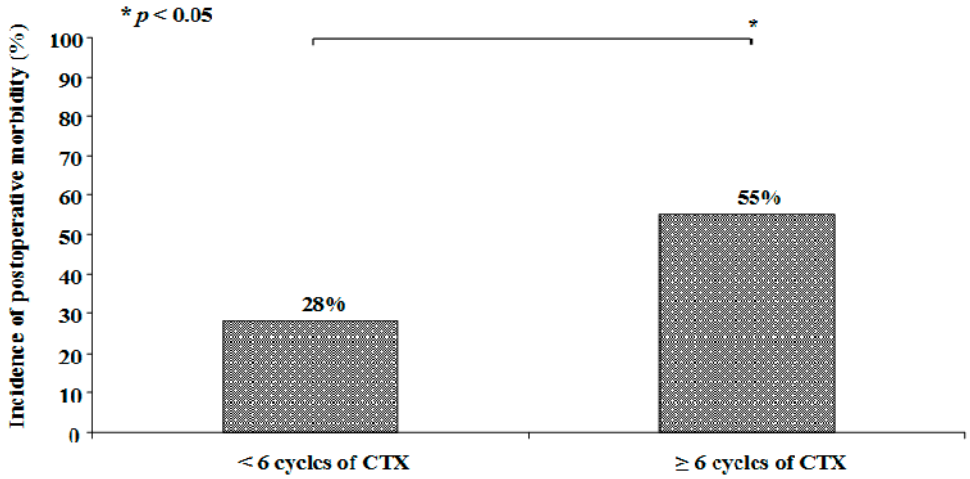

Figure 1: Association between the number of cycles of CTX received (< 6 cycles or ≥ 6 cycles) and the incidence of postoperative complications.

univariate logistic regression models (p< 0.04). Patients who received more than 6 cycles of preoperative chemotherapy presented a higher likelihood of developing postoperative complications (55.1% vs. 28% in patients who received less than 6 cycles) (OR: 3.17; CI95%: 1.01-9.89) (Figure **1**). Time interval from bevacizumab discontinuation to surgery (< 6 weeks or ≥ 6 weeks) was not significantly associated with an increased postoperative morbidity in our analysis (44.4% and 37.5%, respectively) (p= 0.97).

Median follow-up time of patients after liver resection was 41.3 months (range, 26.1-63.9 months). No differences in relapse-free survival were observed according to the preoperative treatment received (p= 0.061). However, a trend to better outcomes was observed in the CTB group. Median relapse-free survival was 10.2 months for the CT group compared with 24.4 months for the CTB group. As for overall survival, there were no differences in this parameter between the two groups of patients considered (p = 0.714). Median overall survival was 52.0 months for the CT group and 58.6 months for the CTB group.

Thirteen patients (61.9%) in the CT group and 20 (60.6%) in the CTB group received adjuvant chemotherapy. Twelve of the 20 patients in the CTB group continued with bevacizumab-containing regimens.

DISCUSSION

In the present study, we observed that bevacizumab did not increase the rate of postoperative complications when compared to the group of patients that received chemotherapy alone and the control group. The number of preoperative chemotherapy cycles received was the only variable associated with postoperative complications in our analysis.

A number of recent retrospective studies have evaluated if the addition of bevacizumab to preoperative chemotherapy increases the risk of peri- and postoperative complications [18-23]. The main finding of those studies, as well as the present study, is that the addition of bevacizumab to preoperative chemotherapy is not related to a higher rate of complications after liver resection. The morbidity rate and the incidence of different postoperative complications in our series were in the range reported in other retrospective studies. There were no differences in the morbidity rate between patients undergoing surgery without preoperative chemotherapy (control group) and the two groups of patients that received preoperative chemotherapy, which is also in line with previous studies [16,24].

We should highlight that the number of patients that received a perioperative blood transfusion in the three groups considered was relatively high. The high number of patients requiring blood transfusions observed also in the control group suggests that the blood management program of the two participating institutions in the present study may account for these figures.

As in other studies, we did not find a statistically significant association between postoperative complications and time interval from bevacizumab discontinuation to surgery (< 6 weeks or ≥ 6 weeks) [19]. Despite these results, we can not rule out an association between time interval from bevacizumab discontinuation to surgery and perioperative complications due to the small sample size analyzed. A long interval between cessation of exposure to bevacizumab and liver resection could prevent postoperative complications related to this molecular-targeted therapy [5,20,23]. In this regard, treatment with bevacizumab should stop at least 6 weeks before liver resection [5]. This time interval is based on the long half-life of bevacizumab, 21 days in mean. If the waiting time is long enough, postoperative complications associated with bevacizumab can be avoided. Although VEGF inactivation is still active 6 weeks after bevacizumab discontinuation, it does not hinder liver regeneration and wound healing according to the results of a study recently published [25].

The number of chemotherapy cycles was significantly associated with an increased postoperative morbidity in our analysis. The prolonged use of preoperative chemotherapy has been related to an increased risk of perioperative morbidity in different studies [13,16]. Thus, prolonged preoperative chemotherapy produces pathologic changes in the liver such as sinusoidal dilatation and atrophy of hepatocytes [13]. Therefore, it is recommended to limit the number of preoperative chemotherapy cycles to allow a safe surgical remove of liver metastases. Some studies have indicated that bevacizumab protects against sinusoidal damage [26,27]. Oxaliplatin-based regimens have been associated with a higher risk of sinusoidal injury complicated by fibrosis and veno-occlusive lesions [14]. Ribero *et al*. observed a lower incidence and severity of hepatic injury when bevacizumab was added to fluoropyrimidine-plus-

oxaliplatin chemotherapy [26]. Similarly, Klinger *et al*. found that the addition of bevacizumab to oxaliplatin-based chemotherapy decreased the severity of sinusoidal obstruction syndrome [27].

As for the efficacy results, we should take into account that only patients who underwent hepatic surgery of colorectal liver metastases were eligible for inclusion in the present analysis and, therefore, clinical response results should be considered carefully. Furthermore, study groups were not completely comparable since it was a heterogeneous population of patients. A trend to a longer relapse free survival was observed in the group of patients who received preoperative bevacizumab. However, postoperative treatment received may account for this observation.

The retrospective nature of the study with its inherent limitations is the main limitation of the analysis. Moreover, definitive conclusions can not be drawn in view of the small number of patients analyzed. Despite these limitations, our results support the evidence that the addition of bevacizumab to preoperative chemotherapy does not increase the risk of complications following surgery of colorectal liver metastases.

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DISCLOSURE

The authors have declared no conflicts of interest.

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