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ORIGINAL ARTICLE

Safety and efficacy of addition of bevacizumab to oxaliplatin-based preoperative chemotherapy in colorectal cancer with liver metastasis- a single institution experience

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Summary

Purpose: *To evaluate the safety and efficacy of the addition of bevacizumab to oxaliplatin-based preoperative chemotherapy in metastatic colorectal cancer (mCRC) patients.*

Methods: *Between August 2008 and December 2011, 51 patients with histologically documented CRC and liver metastases were treated with first-line oxaliplatin-based therapy plus bevacizumab: FOLFOX 4 (oxaliplatin, folinic acid and 5-FU) plus bevacizumab or OXFL mod.Mayo (folinic acid, oxaliplatin and 5-FU) plus bevacizumab.*

Results: *The mean patient age was 59.69± 9.38 years (range 38-78) and 34 (66.67%) were male. Complete response (CR) was achieved in 7 (13.73%) patients, partial response (PR) in 29 (56. 86%) and stable disease (SD) in 6 (11.76%); progressive disease (PD) was registered in 9 (17.65%) patients. Disease control rate was 82.36% (42 patients). Liver resections were performed in 37 (72.55%) patients vs those without resection (p<0.01). The same regimen without bevacizumab was administered postoperatively to 18 (42. 86%) patients. The mean progression free survival (PFS) was 9.90±7.07 months (range 3-26) and was significantly longer in patients with postoperative therapy (p<0.001). Treatment-related toxicity appeared in 28 (54. 90%) patients vs those who did not (p<0.001) Independent of grade, nausea (19.61%), leucopenia (17.65%) and peripheral neuropathy (17.65%) were the most frequent toxicities. Chemotherapy was postponed in 9 (17.65%) patients due to grade 3-4 toxicities. The most frequent grade 3 or 4 toxicities were leucopenia (5.88%) and hypertension (3.92%).*

Conclusion: *Bevacizumab plus oxaliplatin-based treatment is safe and efficient as preoperative treatment of mCRC with primarily unresectable liver metastases. Liver resection could offer a possibility for long-term survival in these patients.*

Key words: *bevacizumab, metastatic colorectal cancer, oxaliplatin based treatment, preoperative treatment*

Introduction

Bevacizumab, a recombinant monoclonal antibody against vascular endothelial growth factor (VEGF), an essential regulator of angiogenesis, has significantly improved the outcome of patients with mCRC [1,2]. Liver is the most common target for metastasis of CRC and resection of liver metastases is an effective treatment in selected patients [3]. The current 5-year overall survival rate after resection of liver metastasis ranges from 25-40% and the increased use of oxaliplatin-based chemotherapy plus bevacizumab has improved patients' survival and the chance of downsizing initially unresectable metastatic disease to allow a curative-intent surgery [4-6]. The combined therapy of bevacizumab with cytotoxic therapy for mCRC improves PFS and duration of response compared with chemotherapy alone [3].

Adverse effects associated with bevacizumab (hypertension, proteinuria and bleeding) are mild–moderate in severity and manageable using standard therapies. Serious toxic effects related to bevacizumab are <5%. The most serious adverse effects that have been reported are arterial thromboembolic episodes and gastrointestinal (GI) bleeding and perforation [7-9].

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Methods

Chemotherapy

Fifty-one patients with histologically documented mCRC with liver metastases were treated with first-line oxaliplatin-based regimes: FOLFOX 4 (Day 1: oxaliplatin 85 mg/m^2 i.v. infusion and folinic acid 200 mg/m^2 i.v. infusion, both given simultaneously over 120 min, followed by 5-FU 400 mg/m^2 i.v. given over 2-4 min, followed by 5-FU 600 mg/m^2 as a 22-h i.v. continuous infusion. Day 2: folinic acid 200 mg/m^2 i.v. infusion over 120 min, followed by 5-FU 400 mg/m^2 i.v. given over 2-4 min, followed by 5-FU 600 mg/m^2 as a 22-h i.v. continuous infusion) plus bevacizumzb 5 mg/kg as 60 min i.v. infusion in 100 mL normal saline every two weeks or OXFL mod.Mayo: (Day 1: oxalipatin 130 mg/m^2 i.v. infusion followed by leucovorin 20 mg/m^2 both given over 120 min and 5-FU 400 mg/m^2 i.v. infusion in 2-4 min. Days 2-5: folinic acid 20 mg/m^2 i.v. infusion over 120 min, followed by 5-FU 280 mg/m^2 i.v. over 2-4 min) plus bevacizumab 7mg/ kg as i.v. infusion over 60 min in 100 mL normal saline every 3 weeks. Patients were treated between August 2008 and December 2011 and analyzed retrospectively. Their performance status (PS) was evaluated by Eastern Cooperative Oncology Group Performance Status Scale (ECOG PS). Responses were analyzed according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Side effects were evaluated according to Common Toxicity Criteria for Adverse Events 3.0. Operability was reassessed every 4 cycles with CT scans.

Surgical technique

Operation was planned 2 weeks after the last dose of chemotherapy and 5-8 weeks between the planned operation and the last bevacizumab dose. Curative liver resection was obligatory and required macro and microscopic complete resection (R0) of the liver lesions. Hepatic metastases were defined as resectable when it was anticipated that they could be completely resected, two adjacent liver segments could be spared, adequate vascular inflow and biliary drainage could be preserved and the volume of the liver remaining post resection could be adequate (at least 25% of the total estimated liver volume). Postoperative therapy with oxaliplatin-based treatment was restarted 5 weeks after the operation (after complete wound healing) and patients received 4 cycles of oxaliplatin-based treatment without bevacizumab.

Statistics

The Statistical Package for Social Sciences v.15.0 (SPSS 15.0) software was used for analysis. Descriptive parameters were expressed as percentages and frequencies, continuous variables were expressed as mean, standard deviation (SD), median (Me), and range. Chi-square test was used for analysis of frequency of some descriptive data. The Shapiro-Wilk test was used for normality analysis of the continuous data. The Mann-Whitney U test and the Spearman's rank correlation coefficient (ρ) were used for testing statistical differences of variables between two groups.

PFS was defined as the time elapsed from the treatment onset until the detection of metastases. Values of $p<0.05$ were considered as statistically significant.

Results

From August 2008 to December 2011, 51 patients with histologically documented CRC plus liver metastases potentially curable by resection, were treated with bevacizumab plus oxaliplatin-based preoperative therapy.

Patient characteristics

The characteristics of the patients are shown in Table 1. Their mean age was 59.69±9.38 years (range 38-78) and their ECOG PS was 0 or 1. Thirty-four (66.67%) were male and 17 (33.33%) female. Carcinoembryonic antigen (CEA) had been evaluated before treatment and 23 patients (45.10%) had baseline CEA levels >5 ng/ml, (upper limit of normal). Synchronous metastatic disease was found in 19 (37.54 %) patients.

Most of the patients (32, 62.75 %) had multiple liver metastases (between 2-4).

Table 1. Patient characteristics

Characteristics	*Patients N*	*%*
Number of patients	51	100
Age, years, median (range)	61 (30-78)	
Gender (M/F)	34/17	66.67/33.33*
Primary site		
Rectum	22	43.14**
Rectosigmoid	6	11.76
Colon	22	43.14**
Sigmoid	1	1.96
ECOG PS		
0	32	62.75**
1	19	37.25
Increased baseline CEA	23	45.10
Synchronous metastatic disease	19	37.57
Number of lesions		
Solitary	13	25.49
2-4	32	62.75**
≥5	6	11.76

ECOG PS: Eastern Cooperative Oncology Group performance status
*p<0.05, **p<0.001

Table 2. Treatment outcomes

Outcomes	*Patients N*	*%*	*Median (range)*	*ρ*
Response				
CR	7	13.73		
PR	29	56.86**		
SD	6	11.76		
PD	9	17.65		
Resection				
Yes	37	72.55*		
No	14	27.45		
Postoperative treatment (N=42)				
Yes	18	42.86		
No	24	57.14		
Chemotherapy cycles			4 (1-14)	
With resection	37	72.55	6 (1-14)	
Without resection	14	27.45	4 (2-10)	
PFS (months)			7 (3-26)	
With postoperative treatment	17	60.71**	17 (5-26)	
Without postoperative treatment	11	39.29	4 (3-15)	
CEA and PFS correlation				-017

* p<0.01, ** p<0.001
ρ: Spearman's rank correlation coefficient

Efficacy

Efficacy is shown in Table 2. CR was achieved in 7 (13.73%) patients, PR in 29 (56.86%), SD in 6 (11.76%) and PD in 9 (17.65%). Disease control rate was 82.36% (42 patients). The mean number of cycles received was 5.29±2.61 (range 1-14). Surgery, defined as curative hepatic metastasectomy, was performed in 37 patients (72.55%) vs 14 (27.45%) patients who didn't achieve resectability (p<0.001). The patients who achieved resectability had the higher number of received cycles (6.71±1.61). Eighteen (42.86%) patients received postoperative chemotherapy.

At the time of analysis, PD was registered in 30 (58.82%) patients. The mean PFS was 9. 90±7.07 months (range 3-26) and it was longer in patients who received postoperative therapy (p<0.001) (Figure 1).

There was no significant correlation between baseline CEA and PFS (ρ = –017).

Toxicity

Toxicities are shown in Table 3. Generally, oxaliplatin-based chemotherapy plus bevacizumab was well tolerated. There were no toxicity-related deaths. Chemotherapy-related toxicity appeared in 28 (54.90%) patients vs 23 (45.1) patients without toxicity (p<0.001). The most frequent toxicities, independent of grade, were nausea (19.61%), leucopenia (17.65%), peripheral neuropathy (17.65%) and diarrhea (13.73%). Chemotherapy was postponed in 9 (17.65%) patients due to grade 3-4 toxicities. The most frequent grade 3 or 4 toxicities were leucopenia (5.88%) and hypertension (3.92%).

Discussion

Our data show that the safety and efficacy profile of bevacizumab plus oxaliplatin-based preoperative treatment in clinical practice are con-

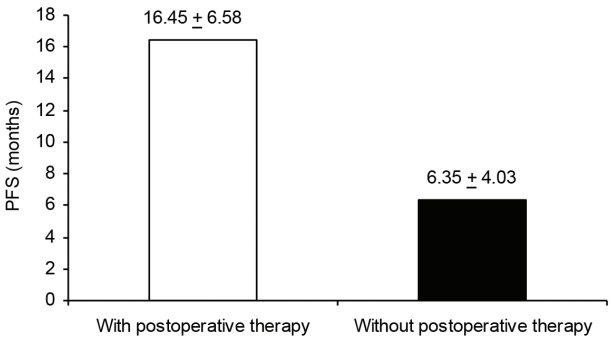

Figure 1. Correlation of progression-free survival between patients who received and did not receive postoperative therapy (p<0.001).

Table 3. Frequency of common toxicities

Chemotherapy related toxicity	*N=28 (54.90%) N (%)*	*Grade 1 N (%)*	*Grade 2 N (%)*	*Grade 3 N (%)*	*Grade 4 N (%)*
Nausea	10 (19.61)	8 (15.69)	2 (3.92)		
Leucopenia	9 (17.65)	3 (5.88)	3 (5.88)	3 (5.88)	
Neuropathy	9 (17.65)	9 (17.65)			
Diarrhea	7 (13.73)	5 (9.80)	2 (3.92)		
Fatigue	3 (5.88)	3 (5.88)			
Vomiting	3 (5.88)	3 (5.88)			
Vertigo	2 (3.92)	1 (1.96)	1 (1.96)		
Epistaxis	2 (3.92)	2 (3.92)			
Hypertension	2 (3.92)			1 (1.96)	1 (1.96)
Rash	1 (1.96)	1 (1.96)			
Neutropenia	1 (1.96)			1 (1.96)	
Urticaria	1 (1.96)			1 (1.96)	
Dyspnea	1 (1.96)			1 (1.96)	
Fever	1 (1.96)		1 (1.96)		
Hemoptysis	1 (1.96)	1 (1.96)			
Anemia	1 (1.96)				1 (1.96)
Thrombocytopenia	1 (1.96)	1 (1.96)			
Melena	1 (1.96)	1 (1.96)			
Constipation	1 (1.96)		1 (1.96)		

sistent with previous observations in prospective randomised clinical trials [1,5,10] and an observational registry study in the United States [11].

The overall response rate seen in 70.59% of our patients was similar in other studies also, such as a multricentric study with CAPOX plus bevacizumab (78%) [12]. Gruenberger et al. reported an objective response rate in 73% of their patients [4]. The TREE study found response rates ranging from 64 to 73%, depending on the oxaliplatin treatment (FOLFOX 6 or CapeOX) [5].The high response rate in our study may be due to metastatic disease being limited to the liver and the overall good PS of the patients.

The low rates of bevacizumab-related adverse effects with the oxaliplatin-based treatment indicate that bevacizumab can be used routinely in clinical practice. The incidence of adverse effects of bevacizumab plus oxaliplatin reported in our analysis was lower than that reported in other trials [2,5-7,11]. The most common chemotherapy-related toxicities were nausea (19.61%), leucopenia (17.65%) and neuropathy (17.65%). Grade 3–4 adverse effects were rare and incuded leucopenia (5.88%) and hypertension (3.92%). Wong et al. reported grade 3/4 hypertension in 4.35% of their patients [12]. We have not found gastrointestinal perforation, bleeding, or other postoperative complications. Grade 3–4 hypertension and hypertension as a serious adverse effect (SAE) had an incidence of 5% in the BEAT trial [7,8] and were reported in 11% (control 2%) and 16% (control 3%) of patients in the studies by Hurwitz et al. [1] and Kabbinavar et al. [13]. The TREE study showed that the addition of bevacizumab to oxaliplatin and fluoropyrimidine treatment had no major impact on toxicity. The incidence of grade 3/4 hypertension in TREE-2 (7-15% grade 3) was higher than in our study but similar to that with bevacizumab 5 mg/kg in combination with FU/LV (9%) or IFL (11% grade 3) as first-line therapy for mCRC [1,5,14]. Our results show that bevacizumab can be added to first-line oxaliplatin-based regimens without altering the toxicity profile of chemotherapy, and with predictable bevacizumab-related toxicity.

In the present study the median number of bevacizumab-containing preoperative cycles was 4 (range 1-14), similar to the reports of other authors [12].

The mean PFS in our trial was 9.9 months, consistent with reports from randomized trials of first-line bevacizumab in mCRC [1,7,13-15] and the BRITE study (9.9 months, 95% CI 9.5-19.3). Our data suggest that the median PFS was significantly higher in patients who received postoperative chemotherapy vs patients who did not (16.45 vs 6.35 months, $p<0.001$). This is in accordance

with the data from the EORTC trial [16] where chemotherapy was associated with a trend toward improved 3-year PFS compared to surgical resection alone.

We confirmed that hepatic metastasectomy after bevacizumab plus oxaliplatin-based treatment is both feasible and safe. In the BEET study, surgery with curative intent after preoperative chemotherapy was performed in 215 (11.2%) of 1914 patients who were considered to be unresectable when metastatic disease was diagnosed. We achieved resectability in 37 (72.55%) of 51 patients, which is much higher than data reported in other studies, with resectability rates around 12.5% after effective chemotherapy [17-19]. This big difference can be explained by preoperative approaches and that patient selection is conceivably a crucial factor. In the BEET and other prospective trials of selected patients with metastases confined to the liver alone, the criteria for non-resectability were most often poorly defined. While in one trial [19], patient inclusion criteria predefined technical non-resectability, in most other studies the definition of non-resectability was left to the discretion of a local surgeon/radiologist, which inevitably limited the comparability of these studies.

Also, in most trials of selected patients, the criteria for non-resectability included other factors that indicated poor prognosis, such as size/number of metastases or presence of synchronous primary CRC and liver metastases [20-22]. This was supported by a recent multivariate analysis that consistently found and reported the prognostic negative influence of the number and size of metastases, the time interval between surgery of the primary tumor and the development of metastases, resection-free margins after primary liver resection and also following preoperative treatment in patients with resectable [21,23] and with initially non-resectable [19] liver metastases.

Bevacizumab is a potent inhibitor of VEGF and its use in the preoperative setting could negatively influence postsurgical wound healing and hepatic regeneration; thus it is recommended that , in order to avoid the negative impact on wound healing or bleeding complications, bevacizumab should be suspended at least 6 weeks before surgery [8,9]. Our data showed that the gap of 5-8 weeks between bevacizumab therapy and liver resection does not increase the rate of complications in patients with mCRC and should not prohibit or delay surgery. In some other studies, the bevacizumab-surgery interval was similar to our study: 6.5-8.5 weeks in a phase I/II study [24] , 7.5-9.5 weeks in the phase I dose-escalation study that involved a higher dose of bevacizumab [25] and 7.1-10.4 weeks in a phase II trial [26]. Gruenberger et al. reported 5 weeks between the last administration of bevacizumab and surgery [4] and Kesmodel et al. reported 7 weeks as a safe interval [3].

The strategy to resect unresectable patients after preoperative effective chemotherapy has been a major breakthrough in the recent history of mCRC with liver metastases alone offering patients under palliative chemotherapy with poor outcome within 3 years a chance of long-term survival. This potential benefit may be obtained with low postoperative mortality (<1%) and acceptable morbidity [19]. Adam et al. reported an actuarial 5-year survival of 35- 40% [18]. With much longer follow-up, survival is currently 33% for 5 years and 22% for 10 years, with a median survival of 39 months [19,20,28]. Very recently, Brouquet et al. reported that post-resection overall survival rate was 60% for 5 years, and 10-year DFS 20% [27].

Surgery remains the gold standard for patients with resectable liver metastases. For patients with non-resectable metastases, improvements in chemotherapy have resulted in significant survival benefit . Encouraging data are now emerging with the combined use of preoperative chemotherapy and surgery [27,28].

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