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Neoadjuvant FOLFIRI + bevacizumab in patients with resectable liver metastases from colorectal cancer: a phase 2 trial

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Background: Preoperative treatment of resectable liver metastases from colorectal cancer (CRC) is a matter of debate. The aim of this study was to assess the feasibility and activity of bevacizumab plus FOLFIRI in this setting.

Methods: Patients aged 18–75 years, PS 0–1, with resectable liver-confined metastases from CRC were eligible. They received bevacizumab 5 mg kg^{-1} followed by irinotecan 180 mg m^{-2}, leucovorin 200 mg m^{-2}, 5-fluorouracil 400 mg m^{-2} bolus and 5-fluorouracil 2400 mg m^{-2} 46-h infusion, biweekly, for 7 cycles. Bevacizumab was stopped at cycle 6. A single-stage, single-arm phase 2 study design was applied with 1-year progression-free rate as the primary end point, and 39 patients required.

Results: From October 2007 to December 2009, 39 patients were enrolled in a single institution. Objective response rate was 66.7% (95% exact CI: 49.8–80.9). Of these, 37 patients (94.9%) underwent surgery, with a R0 rate of 84.6%. Five patients had a pathological complete remission (14%). Out of 37 patients, 16 (43.2%) had at least one surgical complication (most frequently biloma). At 1 year of follow-up, 24 patients were alive and free from disease progression (61.6%, 95% CI: 44.6–76.6). Median PFS and OS were 14 (95% CI: 11–24) and 38 (95% CI: 28–NA) months, respectively.

Conclusion: Preoperative treatment of patients with resectable liver metastases from CRC with bevacizumab plus FOLFIRI is feasible, but further studies are needed to define its clinical relevance.

Twenty percent of patients with colorectal cancer (CRC) have clinical evidence of liver metastases at diagnosis and ~50% of patients will develop liver metastatic disease later (Jemal *et al*, 2004). Surgery is actually an accepted standard approach to liver-confined metastases from CRC. However, unfortunately, 70–80% of patients will relapse in 2 years (Van Cutsem *et al*, 2006). In the

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past 15 years, new drugs, both cytotoxic and biologic agents, have been developed that have resulted in significant improvements in objective response rates and ultimately in overall survival of patients with metastatic CRC. Neoadjuvant chemotherapy has been increasingly used in the management of liver-confined metastases from CRC in the past years, even in patients with initially resectable disease to increase the complete resection rate and treat the micrometastatic disease. In addition, neoadjuvant chemotherapy can be used as a test of *in vivo* chemosensitivity, and patients with extremely aggressive disease, who will progress during preoperative chemotherapy, can be spared useless surgery (Adam *et al*, 2004). Postoperative morbidity and mortality remain the major issues of this approach (Vauthey *et al*, 2006; Van Cutsem *et al*, 2009). In the EORTC 40983 phase 3 trial, a combined approach of pre- and post-operative chemotherapy with FOLFOX (six cycles before surgery and six cycles after) slightly improved progression-free survival with a higher rate of postoperative complications, all reversible, and no difference in preoperative mortality (Nordlinger *et al*, 2008).

The integration of biologic agents into neoadjuvant treatment of liver metastases from CRC has been mostly investigated for the treatment of unresectable metastatic disease (Ellis *et al*, 2005; Saltz *et al*, 2008; Van Cutsem *et al*, 2009; Folprecht *et al*, 2010; Bertolini *et al*, 2011). The feasibility, including perioperative complication rate and potential impact on postoperative liver regeneration, of the combination of bevacizumab with oxaliplatin and capecitabine as preoperative treatment of liver metastases from CRC was evaluated in a single-arm phase 2 study (Gruenberger *et al*, 2008). Bevacizumab was administered up to 5 weeks before surgery. Out of 56 enrolled patients, 52 underwent potentially curative surgery. No patients experienced increased bleeding events or wound-healing complications. Postoperative mortality was null. Normal liver function and regeneration were observed in 98% of the patients who underwent resection. The authors concluded that bevacizumab combined with chemotherapy is a feasible, safe and active neoadjuvant treatment for liver metastases from CRC. The combination of bevacizumab with an irinotecan-based chemotherapy is a standard option in the first-line treatment of metastatic CRC patients (Hurwitz *et al*, 2004). To the best of our knowledge, there are no published data on the use of this combination in the neoadjuvant setting. We report the results of a single-centre, phase II study designed to assess the feasibility and activity of bevacizumab plus FOLFIRI as neoadjuvant treatment of resectable liver-confined metastases from CRC.

PATIENTS AND METHODS

Eligibility and patient evaluation. Patients aged 18 to 75 years, with an Eastern Cooperative Group (ECOG) performance status of 0 or 1, were eligible if they had colorectal adenocarcinoma histologically or cytologically confirmed with resectable liver metastases. Liver disease was defined resectable when the future liver remnant volume would be at least 30% of total liver volume and when two contiguous segments with their own vascularisation and biliary drainage would be preserved. Patients had to have normal organ function and urine dipstick of proteinuria $<2+$ (patients with proteinuria on baseline dipstick urinalysis $\geqslant 2+$ had to undergo a 24-h urine collection and must have had $\leqslant 1$ g of protein per 24 h). Previous adjuvant chemotherapy was allowed if completed >6 months before the enrolment, whereas prior treatment with bevacizumab or irinotecan was not permitted. Patients with distant metastases in organs other than the liver were excluded as well as those who had diagnosis of liver metastases concomitant to the presence of primary CRC producing a stenosis of lumen or a full-thickness bowel wall invasion. Prior history of malignancy other than colorectal, bleeding diathesis, coagulation disorders, clinically significant cardiovascular disease, recent coronary artery disease, serious arrhythmias, regular use of nonsteroidal anti-inflammatory drugs or aspirin (>325 mg day^{-1}) and the presence of ascites were other exclusion criteria. Patients provided written informed consent. The study was approved by the Ethical Committee of the National Cancer Institute of Naples, Naples, Italy.

Treatment. Eligible patients were assigned to receive neoadjuvant FOLFIRI plus bevacizumab. FOLFIRI was administered intravenously (i.v.) every 14 days with irinotecan 180 mg m^{-2} i.v. infusion on day 1, leucovorin 200 mg m^{-2} i.v. infusion on day 1, 5-fluorouracil 400 mg m^{-2} by i.v. bolus on day 1, 5-fluorouracil 2400 mg m^{-2} 46-h continuous infusion; bevacizumab was administered at 5 mg kg^{-1} by i.v. infusion over 90 min at the first cycle, and then, if tolerated, over 60 min. The treatment was administered every 14 days, for 7 cycles; bevacizumab was stopped at cycle 6 to prolong the bevacizumab-free interval and to reduce the risk of surgical bleeding.

After restaging, patients whose liver metastases were still confirmed as potentially resectable underwent surgery.

Following surgery, four further cycles of FOLFIRI plus bevacizumab were planned, with the same dose and schedule planned.

Assessment of outcomes. Baseline assessment included medical history, physical examination, haematology, biochemistry, proteinuria and blood pressure measurement; all these were repeated before each cycle of treatment. All patients were evaluated by a multidisciplinary team composed of an oncologist, a surgeon and a radiologist at diagnosis and after neoadjuvant chemotherapy before performing surgery. A surgical evaluation to define liver metastases as potentially resectable was expected at baseline. Electrocardiogram was performed at baseline and then every two cycles.

Tumour response was assessed with computed tomographic scan after neoadjuvant treatment using RECIST criteria version 1.0. As an exploratory substudy, two FDG PET/CT scans were included within the flow of examinations planned by the protocol; results of the substudy will be reported elsewhere.

Liver resection was defined as radical (R0) according to both macroscopic description of surgery and histological evaluation. Radical surgery was defined as a margin of at least 1 mm. Pathologic response was classified according to the Mandard system (Mandard *et al*, 1994).

Toxicity was assessed according to the Common Toxicity Criteria Adverse Events 3.0.

Study design. A single-stage, single-arm, phase 2 study design was applied. With 39 patients enrolled, the study would be powered to describe an expected proportion of $70 \pm 12\%$ rate of patients alive and disease free at 1 year. Secondary end points were the incidence of postoperative complications and the antitumour activity in terms of overall response rate to preoperative chemotherapy. All descriptive analyses were done on the basis of intention to treat.

RESULTS

From October 2007 to December 2009, 39 patients with liver metastases from colon (87.2%) or rectal (12.8%) cancer were enrolled in a single institution. Of these, 27 (69.2%) patients were diagnosed with a metastatic disease. Out of the 12 patients with a previous diagnosis, 5 (12.8%) patients had adjuvant chemotherapy (FOLFOX-4 for 12 cycles) after resection of the primary tumour. Median age was 58 (range 30–75); males were prevalent (61.5%). The most frequent comorbidity at enrolment was hypertension, reported in 38.5% of patients. For two patients, liver metastases

were erroneously defined as operable at registration; these patients received planned medical treatment and have been considered in the following analyses. One further patient, who had been previously operated for primary colon cancer, was found ineligible *a posteriori*, because pathologic examination of the resected liver lesion revealed a primary liver cancer, not a metastasis from CRC. This patient too was considered in the analyses. Baseline characteristics of patients and of the disease are summarised in Table 1.

A total of 37 (94.9%) patients received 6 injections of bevacizumab associated with the first 6 cycles of chemotherapy; 1 stopped bevacizumab after 4 administrations (because of thrombosis) and 1 received bevacizumab also combined to the seventh administration of chemotherapy because it was clear that surgical resection of liver metastases could not be attempted. Bevacizumab median dose intensity was 1.7 (range 1.5–2.3) $mg\,kg^{-1}$ per week, with a relative dose intensity of 69% (range 60–29). All the patients received seven administrations of chemotherapy, as planned. Irinotecan median dose intensity was 70 (range 41–88) $mg\,m^{-2}$ per week, with a relative dose intensity of 78% (range 45–98). Overall time required to conclude the planned treatment was quite longer than the 14 planned weeks; median actual time was 18 weeks (range 14–20). Reasons for dose delaying were grade 3 neutropenia for 6 patients (15%), CVC-related complication for 4 patients (10%) and diarrhoea for 2 patients (5%). In 11% of cases, the delay was due to logistic reasons. As a consequence, although dose reductions of bevacizumab were never done and only one patient had a 50% reduction of dose of chemotherapy because of severe haematologic toxicity, median dose intensity of bevacizumab and of irinotecan (considered as indicative for all the cytotoxic drugs) was reduced as compared with the planned one: 69% (range 60–92) and 78% (range 45–98), respectively.

During neoadjuvant treatment, neutropenia was the most frequent adverse event (23.1% of patients), grade 3 in 6 cases (15.4%). Granulocyte colony-stimulating factor (G-CSF) was used in 8 patients: 6 had grade 3 neutropenia and received G-CSF to maintain dose intensity, 1 had febrile neutropenia and 1 had persistent grade 2 neutropenia; erythropoietin was used in 1 patient with grade 2 anaemia. Three patients (two of which already suffering hypertension at baseline) had grade 3 hypertension. Diarrhoea was also frequent (23.1% of patients) but severe in only 2 cases (Table 2).

All patients underwent radiologic restaging after neoadjuvant treatment, before planned surgery. At CT scan evaluation, according to RECIST, 1 patient (2.6%) had a complete response and 25 a partial response (64.1%) for an overall objective response rate of 66.7% (95% exact CI: 49.8–80.9). Two patients (5.1%) progressed but were still considered operable. Both the two patients identified as nonoperable shortly after treatment start had stable disease and did not undergo liver surgery.

In all, 37 patients (94.9%) were operated to resect liver metastases, with a median interval of 9 weeks from the last administration of bevacizumab and 6 weeks from the last administration of chemotherapy. More than half of the operations were resection of one or two hepatic segments; radiofrequency ablation of lesions with a maximum diameter of 2 cm was associated in 8 patients and was always considered radical, meaning nonresidual tumour left, as it was performed by needle for treating 4 cm of liver tissue.

Radical surgery (R0) was achieved in 33 (84.6%) of the enrolled patients. Five patients (12.8%) had a pathological complete remission and were classified as Tumour Regression Grade (TRG) 1 according to Mandard system. Twelve patients (30.8%) had a pathological partial remission (including TRG 2 and 3 according to Mandard system). Out of the four patients not radically resected, three underwent major surgery but had surgical margins positive for malignant cells, whereas one patient had only explorative laparotomy because of the presence of peritoneal carcinomatosis that was not evident at CT scan.

Out of 37 patients who underwent surgery, 16 (43.2%) had at least one adverse event after surgery; the most frequent were biloma (12 patients, 32.4%) and pleural effusion (3 cases, 8.1%). The majority of bilomas (10 patients) were clinically silent (<4.0 cm in max diameter) and were observed at the 30-day

Table 1. Baseline characteristics ($n=39$)

Age, median (range), years	58 (30–75)
Gender, *n* (%)	
Male	24 (61.5)
Female	15 (38.5)
Comorbidities and previous pathologic conditions, *n* (%)	
Controlled hypertension	15 (38.5)
Controlled diabetes	7 (17.9)
Episodes of hypersensitivity	5 (12.8)
Gastric ulcer	2 (5.1)
Degenerative arthropathy	2 (5.1)
COPD	2 (5.1)
Site of cancer at first diagnosis, *n* (%)	
Colon	34 (87.2)
Rectum	5 (12.8)
Previous surgery on primary tumour, *n* (%)	
Total	34 (87.2)
Left hemicolectomy	14 (35.9)
Anterior resection of rectum	12 (30.8)
Right hemicolectomy	8 (20.5)
No. of target lesions at baseline, *n* (%)	
1	14 (35.9)
2	7 (17.9)
3	6 (15.4)
4	3 (7.7)
5	4 (10.3)
$\geqslant 6$	5 (12.8)

Abbreviation: COPD = chronic obstructive pulmonary disease.

Table 2. Worst degree of toxicity

Adverse events	Any grade, *n* (%)	Grade 3, *n* (%)
Neutropenia[a]	9 (23.1)	6 (15.4)
Hypertension	16 (41.0)	3 (7.7)
Nausea	6 (15.4)	3 (7.7)
CVC-related complications	4 (10.3)	4 (10.3)
Diarrhoea	9 (23.1)	2 (5.1)
Fatigue	3 (7.7)	1 (2.6)
Febrile neutropenia	1 (2.6)	1 (2.6)
Anaemia	2 (5.1)	0 (0)
Bleeding	2 (5.1)	0 (0)
Stomatitis	2 (5.1)	0 (0)

Abbreviation: CVC = central venous catheter.
[a]Only grade >1 toxicity reported.

Table 3. Surgery after neoadjuvant treatment	
Type of surgery by site, *n* (%)	
Not performed	2 (5.1)
Primary tumour	3 (7.7)
Left hemicolectomy	1 (2.6)
Right hemicolectomy	1 (2.6)
Anterior resection of rectum	1 (2.6)
Metastases	37 (94.9)
Bi-segmentectomy	14 (35.9)
Segmentectomy	7 (17.9)
Left hepatectomy	5 (12.8)
Right hepatectomy	2 (5.1)
Enlarged right hepatectomy	2 (5.1)
Wedge resection	1 (2.6)
Other partial hepatic resections	6 (15.4)
Time from last bevacizumab, median (range), weeks	9 (6–15)
Time from last chemotherapy, median (range), weeks	6 (3–13)
Radiofrequency ablation associated, *n* (%)	8 (21.6)
Surgical outcome, *n* (%)	
R0	33 (84.6)
R1	2 (5.1)
R2 + not operable	4 (10.3)
At least one surgery-related toxicity, *n* (%)	
No	21 (56.8)
Yes	16 (43.2)
Surgery-related toxicity, *n* (%)	
Biloma	12 (32.4)
Pleural effusion	3 (8.1)
Hepatic abscess	1 (2.7)
Fistula	1 (2.7)
Common bile duct injury	1 (2.7)
Pancreatitis	1 (2.7)
Wound dehiscence	1 (2.7)

postsurgical control CT scan; only in two cases, biloma aspiration was necessary (Table 3).

After liver surgery, 28 (71.8%) patients started medical treatment again, with combined bevacizumab plus FOLFIRI; 25 of them received 4 cycles as planned and 3 received 2 cycles only because of progression (1 case) and toxicity (2 cases: fatigue and CVC infection). Eleven patients were not candidate to resume medical treatment after liver surgery because of surgical complications (4 cases), progressive disease or R2 at surgery (2 cases), not operated (2 cases), finding of hepatocellular carcinoma histology, central venous catheter complications and death because of myocardial infarction 40 days after surgery (1 case each).

At 1 year of follow-up, the time designated for testing the primary end -point of the study, 24 patients were alive and free from disease progression (61.6%, 95% CI: 44.6–76.6).

On April 2012, 19 patients had died and 31 patients had an event according to the PFS definition. Median PFS was 14 months (95% CI: 11–24) and median OS was 38 months (95% CI: 28–NA); PFS and OS curves are shown in Figure 1.

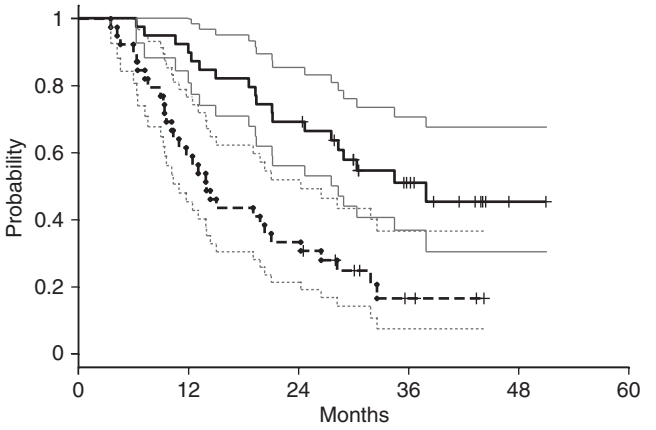

Figure 1. Kaplan–Meier estimated PFS (dashed line) and OS (solid line) curves, with 95% confidence limits. Vertical dashes represent censored patients.

DISCUSSION

To the best of our knowledge, this is the first study that has evaluated the feasibility and activity of the combination of bevacizumab with an irinotecan-based chemotherapy as preoperative treatment of initially resectable liver metastases from CRC.

Compared with the previous oxaliplatin-based studies in the same setting (Gruenberger *et al*, 2008; Nordlinger *et al*, 2008), we observed a higher incidence of postoperative morbidity. In our study, 44% of the patients experienced at least one postoperative adverse event compared with 25% of the patients in previous oxaliplatin-based studies. The incidence of adverse events possibly related to bevacizumab was negligible and comparable to other studies. The difference in incidence of adverse events seems related to a quite high rate of biliary complications (32% in our study *vs* 2% in previous studies). However, all such complications were reversible and most were clinically nonsignificant. A high rate of radiofrequency ablations associated with major liver surgery in our study and the possible lack of reporting clinically irrelevant events in the other studies (Gruenberger *et al*, 2008; Nordlinger *et al*, 2008) could explain this difference. Our data, however, are consistent with a case-controlled study on the safety of neoadjuvant bevacizumab and chemotherapy for liver metastases from CRC, where 44% of the patients treated with bevacizumab had postoperative complications (Tamandl *et al*, 2010).

In our study, one patient died 40 days after surgery for myocardial infarction, after good postsurgical recovery and when he was apparently well. We believe that this event is more likely because of a combination of several cardiologic risk factors such as diabetes mellitus, hypertension and a strong familiarity for ischaemic heart disease rather than previous administration of bevacizumab. However, cases of myocardial infarction have been possibly related to bevacizumab therapy in large observational studies (Kozloff *et al*, 2010; Bertolini *et al*, 2011).

These results confirm that the addition of bevacizumab to standard chemotherapy as neoadjuvant treatment of resectable liver metastases from CRC does not increase clinically relevant postoperative morbidity and that at least a 6-week gap from the last administration of bevacizumab and surgery is a safe interval (Gruenberger *et al*, 2008; Bertolini *et al*, 2011).

In our study, the rates of objective response, disease control and radical surgery (R0) were encouraging, the complete pathological remission rate was particularly elevated, but the 1-year progression-free rate (our primary end point) was lower than the planned one. Also, the median PFS survival of 14 months in our study is lower than the 18.7 months reported in the EORTC study (Nordlinger *et al*, 2008). However, a significant portion of patients enrolled in our study had unfavourable prognostic factors; in particular, 25% of patients had more than five metastatic lesions and needed major surgery and 70% of patients had a synchronous metastatic tumour. In the EORTC study, patients had to have four

or less metastatic lesions and 78% had one or two deposits to the liver. Moreover, in the EORTC study, only 34% of patients had a synchronous metastatic tumour. In addition, consistent with the intention-to-treat strategy, we also included three patients who were actually found ineligible after registration and might have shortened PFS. Despite all the limits of comparing results of different studies, overall, our results seem similar to the previous ones obtained with the oxaliplatin-based combinations (Gruenberger *et al*, 2008; Nordlinger *et al*, 2008) and further suggest the potential usefulness of bevacizumab and chemotherapy in the perioperative setting.

In conclusion, our study suggests that a neoadjuvant treatment with an irinotecan-based chemotherapy and bevacizumab is feasible and potentially active for patients with initially resectable liver metastases from CRC, but further clinical trials are needed to define whether such a treatment may be considered a reasonable option in clinical practice.

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APPENDIX

The following co-authors (belonging to the Naples Colorectal Cancer Group) contributed to this study.

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