Bevacizumab Improves Pathologic Response and Protects Against Hepatic Injury in Patients Treated With Oxaliplatin-Based Chemotherapy for Colorectal Liver Metastases

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BACKGROUND. The current study evaluated the effect of bevacizumab added to fluoropyrimidine-plus-oxaliplatin (5FU/OX) chemotherapy for colorectal liver metastases (CLM) on the pathologic response and nontumorous liver histology.

METHODS. A total of 105 consecutive patients treated preoperatively with 5FU/OX chemotherapy with (n = 62) or without (n = 43) bevacizumab were analyzed. The response to chemotherapy was evaluated by pathologic analysis of tumor viability (percentage of viable tumor in relation to tumor surface area). The incidence and grade of hepatic sinusoidal dilation were also investigated.

RESULTS. Bevacizumab-containing regimens significantly reduced the degree of tumor viability compared with 5FU/OX-only chemotherapy (32.9% vs 45.3%; $P = .02$). After stratification according to the magnitude of tumor viability, a higher proportion of patients treated with bevacizumab than without had <25% residual viable tumor cells (45% vs 23%; $P = .02$). However, the addition of bevacizumab to 5FU/OX did not appear to increase the incidence of complete pathologic response (11.3% vs 11.6%; $P = .59$). The incidence and severity of sinusoidal dilation was lower in patients treated with bevacizumab than in those treated with 5FU/OX only (any grade: 27.4% vs 53.5%; moderate or severe: 8.1% vs 27.9%; both $P < .01$).

CONCLUSIONS. In patients treated with 5FU/OX chemotherapy, bevacizumab improves the pathologic response, as demonstrated by a reduction of the degree of tumor viability, and reduces the incidence and severity of hepatic injury. This retrospective study provides additional evidence supporting the use of bevacizumab in combination with 5FU/OX for CLM. ***Cancer* 2007;110:2761–7.** © *2007 American Cancer Society.*

KEYWORDS: oxaliplatin, bevacizumab, tumor response, colorectal liver metastases, sinusoidal dilatation, hepatotoxicity.

In recent years, preoperative systemic chemotherapy has been used in patients with colorectal liver metastases (CLM) to downsize unresectable tumors and make hepatic resection possible,[1–3] and to identify responders so that patients can be spared nonbeneficial surgical treatment and ineffective postoperative chemotherapy.[4–6] The clinical relevance of the radiographic response to chemotherapy,

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defined as a reduction of tumor size, is also emphasized by its conventional use for treatment efficacy assessment.[7] However, this simple, macroscopic criterion for tumor response evaluation may not be enough per se to determine the effectiveness of a treatment.[8] Pathologic analysis of tumor viability represents an alternative method to evaluate tumor response after preoperative treatments. Recent data indicate that preoperative chemotherapy results in a reduction or disappearance of viable tumor cells,[9] and assessment of residual viable tumor cells has been used to compare the efficacy of different preoperative treatments.[10]

As more patients receive preoperative systemic chemotherapy, clinically significant chemotherapy-specific hepatic injuries are increasingly being reported.[4,11–13] We recently reported a 20% incidence of steatohepatitis in association with irinotecan-based chemotherapy and a 19% incidence of sinusoidal injury after treatment with oxaliplatin.[4] In 2 series reporting on patients who received mostly oxaliplatin-based preoperative chemotherapy, the authors reported a higher rate of sinusoidal injury and an increase in perioperative blood transfusions and surgical complications in patients who received preoperative chemotherapy than in those who did not.[11,12]

In patients with advanced metastatic colorectal cancer, targeted biologic therapy with bevacizumab, a recombinant human monoclonal antibody to vascular endothelial growth factor-A (VEGF-A), has recently been used in association with 5-fluorouracil, irinotecan, and oxaliplatin. Preliminary data from these studies indicate an increase in radiologic response rate and survival with the combination of bevacizumab and cytotoxic chemotherapy.[14–16] However, to our knowledge, the efficacy of bevacizumab in combination with chemotherapy in patients undergoing preoperative chemotherapy followed by liver resection has not been published to date, and it is not known whether the combination of bevacizumab and cytotoxic therapy improves pathologic response or affects hepatic injury of the nontumorous liver.[4,11]

The objective of the current study was to determine the effect of bevacizumab added to fluoropyrimidine-plus-oxaliplatin chemotherapy administered before hepatic resection for CLM. To achieve this objective, we reviewed a consecutive series of patients who received preoperative fluoropyrimidine-plus-oxaliplatin chemotherapy with or without bevacizumab to answer the following questions: Does bevacizumab 1) increase the response of CLM as measured by systematic pathologic analysis of tumor viability? and 2) affect the incidence of sinusoidal dilation?

MATERIALS AND METHODS

From the hepatobiliary database of the University of Texas M. D. Anderson Cancer Center, we identified 105 consecutive patients who underwent liver resection for CLM after preoperative fluoropyrimidine-plus-oxaliplatin (5FU/OX) chemotherapy with or without bevacizumab between November 2002 and July 2006. In the group that received bevacizumab, the last dose was administered 6 or more weeks before surgery.[17] With the aim of maximizing tumor response, 1 additional cycle of 5FU/OX was usually administered after bevacizumab was discontinued. To ensure homogeneity within groups, patients treated at any time before hepatic resection with drugs other than fluoropyrimidines, oxaliplatin, and bevacizumab were excluded. This study was approved by our Institutional Review Board (IRB #RCR06-0712).

Demographic and clinical data were obtained by reviewing medical records. A single gastrointestinal pathologist with hepatobiliary expertise (H.W.), blinded to the chemotherapy regimens with which individual patients had been treated, evaluated the resected specimens. Nontumorous liver tissue was reviewed to define the presence and grade of sinusoidal dilation according to a previously reported standard 4-point scale on which 0 indicated the absence of sinusoidal dilation, 1 indicated mild sinusoidal dilation (centrilobular involvement limited to approximately one-third of the lobular surface), 2 indicated moderate sinusoidal dilation (centrilobular involvement extending in approximately two-thirds of the lobular surface), and 3 indicated severe sinusoidal dilation (complete lobular involvement).[4,18] The tumoricidal effect of chemotherapy was analyzed using a previously defined methodology[19] as follows. On routine hematoxylin & eosin-stained sections the area of residual viable tumor cells within each metastatic nodule was estimated as a percentage of the total tumor surface area that includes areas of coagulative necrosis, calcification, fibrosis, and the associated histiocytes, foreign body giant cells, and inflammatory cells (Fig. 1). All archival slides, for an average of 2 to 3 sections per tumor nodule, were reviewed. When multiple tumors were present, the mean percentage was used.

Continuous variables, presented as means with standard error of the mean unless otherwise stated, were compared using the Mann-Whitney *U* test; discrete variables, expressed as the number and percentage, were compared using the chi-square test or Fisher exact test, when appropriate. Statistical significance was defined as $P < .05$.

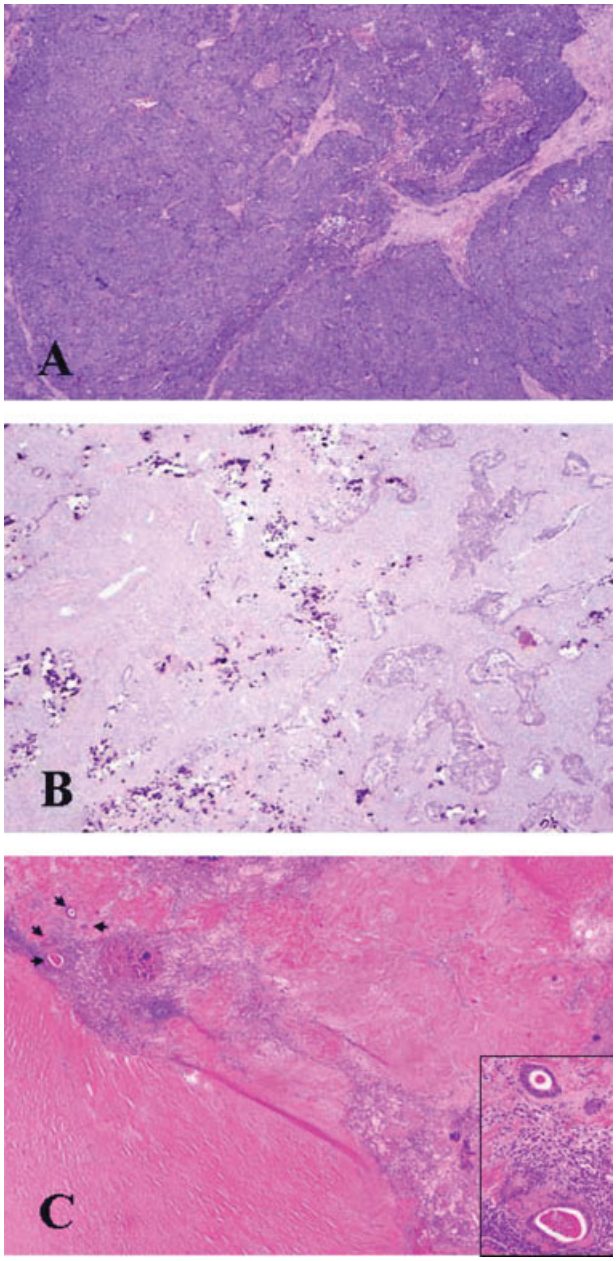

FIGURE 1. Representative photomicrographs of metastases demonstrating different percentages of residual viable tumor cells. (A) Approximately 90% residual viable tumor cells. (B) Approximately 50% residual viable tumor cells. (C) Extensive fibrosis, necrosis, calcifications, and the associated collections of histiocytes and inflammatory cells with 1% viable tumor cells (marked with arrows and shown in the *inset*) (H & E, original magnification ×20; *inset*: ×200).

RESULTS

Forty-three patients received 5FU/OX without bevacizumab and 62 received 5FU/OX with bevacizumab. Clinical and pathologic characteristics for the patients in the 2 study groups are shown in Table 1.

TABLE 1
Clinical and Pathologic Features of Patients*

Variable	5FU/OX (n = 43)	5FU/OX plus bevacizumab (n = 62)	P
Median age (range), y	57 (26–80)	53.5 (34–85)	.61
Gender			
Male	26 (60)	36 (58)	.80
Female	17 (40)	26 (42)	
BMI			
Median (range), kg/m^2	27.1 (14.7–38.3)	27.5 (17.9–50.7)	.89
>25 kg/m^2	31 (72)	37 (60)	
Coexisting diabetes	4 (9)	8 (13)	.98
Site of primary tumor			
Colon	32 (74)	43 (69)	.57
Rectum	11 (26)	19 (31)	
Status of primary lymph nodes			
Positive	32 (74)	44 (71)	.95
Not available	2 (5)	6 (10)	
Synchronous hepatic metastases†	32 (74)	34 (55)	.12
Median no. of cycles of preoperative chemotherapy (range)	6 (2–16)	6 (3–12)	.46
Mean (SEM) interval time between completion of chemotherapy and surgery, mo‡	1.71 (0.153)	1.99 (0.156)	.15
Median largest tumor dimension (range), cm§	3.5 (1–10)	2 (0.5–12)	.004
Colorectal liver metastases			
Median no. (range)	2 (1–8)	2 (1–21)	.33
Solitary metastasis	16 (37)	22 (35)	.85

5FU/OX indicates fluoropyrimidines plus oxaliplatin; BMI, body mass index; SEM, standard error of the mean.

* Values in the table are shown as the number of patients (percentages) unless otherwise indicated.

† Disease-free interval of <1 month.

‡ Data were not available for all patients.

§ Calculated using the size of the largest lesion when multiple colorectal liver metastases were present.

Pathologic Response

A total of 285 tumor nodules were reviewed. Pathologic analysis revealed that treatment with 5FU/OX only was associated with significantly greater percentage of residual viable tumor cells compared with treatment with 5FU/OX plus bevacizumab (45.3% ± 3.7 vs 32.9% ± 3.5; $P = .02$) (Fig. 2A). When patients were stratified according to the magnitude of tumor viability (<25%, 25–49%, 50–75%, and >75% of total tumor surface area), a significantly higher proportion of patients treated with bevacizumab had <25% residual viable tumor cells compared with patients who were not treated with bevacizumab (45% vs 23%; $P = .02$). A complete pathologic response (ie, no identifiable viable tumor cells in any tumor nodules) was observed in 5 patients (11.6%) treated with 5FU/OX only for a median of 12 cycles (range, 4–15 cycles) and 7 patients (11.3%) treated with 5FU/OX plus bevacizumab for a median of 4 cycles (range, 4–12 cycles) ($P = .59$). It is

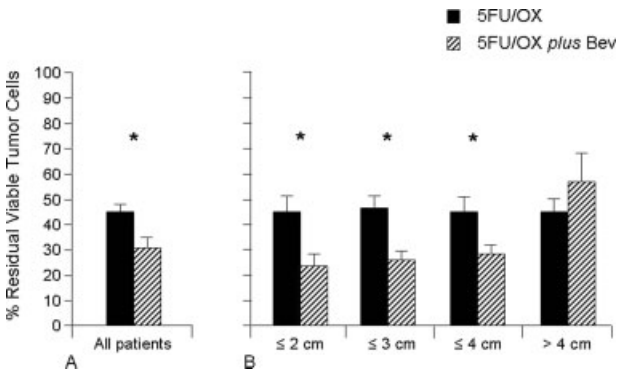

FIGURE 2. Percentage of residual tumor cells after preoperative chemotherapy with fluoropyrimidine plus oxaliplatin only (5FU/OX) and 5FU/OX plus bevacizumab (5FU/OX plus Bev). (A) Overall results. (B) Results for subgroups stratified according to posttreatment tumor dimension as measured on macroscopic pathology. *$P < .05$.

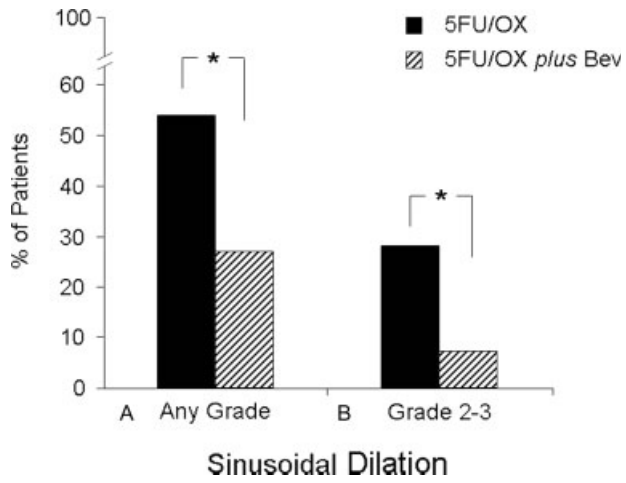

FIGURE 3. Incidence of (A) sinusoidal dilation of any grade and (B) moderate or severe (grade 2 or 3) sinusoidal dilation after preoperative chemotherapy with fluoropyrimidines plus oxaliplatin only (5FU/OX) or 5FU/OX plus bevacizumab (5FU/OX plus Bev). *$P = .006$.

interesting to note that the mean dimension, measured on macroscopic pathology, of the 26 metastases found in these 12 patients was 2 cm ± 0.5 cm (median, 1.9 cm) despite the absence of viable tumor cells.

There were a wide range of tumor sizes resected in both groups (median, 2 cm [range, 0.5–12 cm] in the bevacizumab group, and 3.5 cm [range, 1–10 cm] in the 5FU/OX group). To investigate whether resected tumor dimension might be associated with the degree of pathologic response, patients were stratified according to tumor dimension as measured on macroscopic pathology for the following subgroups: ≤2 cm, ≤3 cm, ≤4 cm, and >4 cm (the number of patients compared in each stratum were 40, 47, 54, and 8, respectively, in the bevacizumab group and 16, 21, 28, and 15, respectively, in the 5FU/OX group) (Fig. 2B).

Treatment with bevacizumab was associated with significantly reduced percentages of residual viable tumor cells in each subgroup (≤2 cm: 24.6% ± 3.7 [median, 20%] vs 45.6% ± 6.6 [median, 50%] [$P = .01$]; ≤3 cm: 25.9% ± 3.7 [median, 20%] vs 46.2% ± 5.2 [median, 50%] [$P = .003$]; and ≤4 cm: 29.5% ± 3.5 [median, 30%] vs 45.4% ± 5.1 [median, 50%] [$P = .01$]). When considering patients with tumors >4 cm, no difference was found between patients treated with and those treated without bevacizumab with regard to tumor viability (58.5% ± 10.7 [median, 70%] vs 45.3 ± 5.3 [median, 50%]; $P = .09$).

Overall, treatment duration was similar between the groups treated with and those treated without bevacizumab. To clarify the effect of the duration of chemotherapy on pathologic response, patients were stratified according to the number of cycles of 5FU/OX received (2–4 [42 patients], 5–8 43 patients]; and >8 [20 patients]). The distribution of patients across these subgroups was similar between the 2 treatment groups (5FU/OX with or without bevacizumab). Patients treated without bevacizumab had greater percentages of residual viable tumor cells than those treated with bevacizumab regardless of the duration of treatment (2–4 cycles: 50% ± 5.3 [median, 50%] vs 35.5% ± 6.2 [median, 30%]; 5–8 cycles: 46.2% ± 5.9 [median, 55%] vs 32.7% ± 4.3 [median, 30%]; and >8 cycles: 32.5% ± 9.9 [median, 45%] vs 28.18% ± 9.2 [median, 5%], respectively) (differences did not reach statistical significance in these subgroup analyses).

Incidence of Sinusoidal Dilation

Pathologic review of the nontumorous liver parenchyma revealed that the incidence of sinusoidal dilation of any grade was significantly higher in patients treated without bevacizumab (23 of 43 patients; 53.5%) than in those treated with bevacizumab (17 of 62 patients; 27.4%) ($P = .006$) (Fig. 3A). The incidence of moderate or severe sinusoidal dilation was also significantly higher in patients treated without bevacizumab (12 of 43 patients; 27.9%) than in those treated with bevacizumab (5 of 62 patients; 8.1%) ($P = .006$) (Fig. 3B). These differences were independent of the duration of chemotherapy. The median number of cycles of 5FU/OX was similar in patients who developed any grade of sinusoidal dilation (6 cycles; range, 2–16 cycles) and those who did not (6 cycles; range, 2–15 cycles) and in those who developed moderate to severe sinusoidal dilation (6.5 cycles; range, 2–13 cycles) and those who did not (6 cycles; range, 2–16 cycles) (both $P > .05$).

DISCUSSION

In this study, we found that 5FU/OX plus bevacizumab was oncologically more effective than 5FU/OX alone as demonstrated by the greater pathologic responses assessed in resected tumors. We also found that the incidences and severity of hepatic injury were reduced when bevacizumab was added to 5FU/OX. These findings provide additional evidence supporting the use of bevacizumab for CLM.

To our knowledge, this is the first study to analyze the pathologic effect of preoperative chemotherapy with 5FU/OX plus bevacizumab on resected CLM and nontumorous liver. Previous studies have examined the efficacy of bevacizumab added to cytotoxic therapy using clinical outcome measures,[14,15] but analysis of pathologic changes that occur in tumors after treatment with biologic agents is lacking.

Our decision to evaluate tumor response pathologically was motivated by recent reports that suggest that radiologic assessment of changes in tumor size may not accurately reflect response to chemotherapy[8] and may either overestimate[20] or underestimate the actual extent of tumor regression.[18] (Fig. 4) Two studies focused on targeted biologic therapies have further emphasized these limitations[21] and demonstrated that in some disease types changes in tumor size in response to biologic therapies underestimate the actual pathologic tumor response.[22] One possible explanation is that radiologic methods cannot fully differentiate between areas of viable tumor and areas of fibrotic replacement induced by effective chemotherapy. (Fig. 4)

A recent study by Rubbia-Brandt et al.[9] provides new insights into the pathologic changes induced by oxaliplatin-based chemotherapy and provides a framework within which the findings of the current study can be analyzed. The findings of that study demonstrated that, compared with tumors not treated with preoperative chemotherapy, tumors treated with preoperative oxaliplatin exhibit significant tumor regression with marked reduction or disappearance of viable tumor cells and fibrosis overgrowth.[18] In the current study, we confirmed the finding of Rubbia-Brandt et al. that tumor response to chemotherapy is characterized, in part, by replacement of tumor with fibrosis (Fig. 1C). Furthermore, we found not only that a similar pathologic change occurs in tumors treated with 5FU/OX plus bevacizumab, but the addition of bevacizumab to 5FU/OX yielded an incrementally greater decrease in residual viable cells within the resected tumors over the decrease associated with 5FU/OX alone. It is interesting to note that this differentially greater pathologic response with bevacizumab was significant in tumors measuring $\leq$4 cm and was independent of the duration of chemotherapy. The absence of improved response in tumors measuring $>$4 cm may be related to the inadequate sample size to detect the difference, or to the lesser effectiveness associated with bevacizumab for this subset. These data also suggest that the improved tumor regression with bevacizumab occurs early during treatment and that a fairly stable benefit is sustained with increasing duration of treatment.

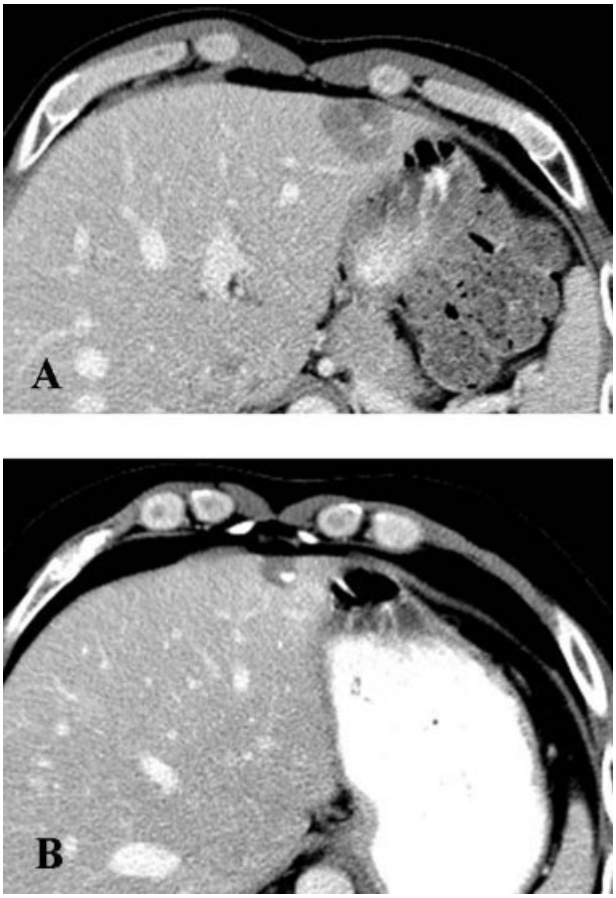

FIGURE 4. Pathologic response to preoperative treatment with fluoropyrimidines plus oxaliplatin (5FU/OX) and bevacizumab in a patient aged 36 years with synchronous bilobar liver metastases from pT3 pN1 sigmoid adenocarcinoma who was a candidate for a 2-stage hepatectomy. (A) Before chemotherapy, the patient had a metastasis measuring 3.4 cm in segment 3 of the liver. (B) Partial radiographic response of the metastasis in segment 3 after 3 cycles of 5FU/OX and bevacizumab (dimension of 1.5 cm). At this time, the patient underwent wedge resection of the metastasis in segment 3 (first-stage surgery). A representative photomicrograph of this metastasis is shown in Figure 1C.

Increased pathologic response to preoperative treatment is associated with improved long-term outcome in several malignancies, such as esophageal cancer and colorectal cancer.[19,23] A similar survival

advantage has been recently reported in patients with CLM treated with 5-fluorouracil, oxaliplatin, or irinotecan.[9] However, whether the degree of improved pathologic response associated with bevacizumab for CLM translates into improved long-term outcome remains to be evaluated by further study.

The second major finding of this study was that bevacizumab reduced the incidence and severity of oxaliplatin-related sinusoidal dilation. Oxaliplatin-based chemotherapy has been shown to cause hepatic sinusoidal dilation,[4,12,18] a vascular injury characteristic of veno-occlusive disease,[24] recently renamed sinusoidal obstruction syndrome (SOS).[25] SOS is a complication of conditioning chemotherapy before bone marrow transplantation in 5% to 54% of patients.[26–28] Although to our knowledge the pathophysiology of drug-induced SOS is not fully understood, in vitro and in vivo models suggest that oxaliplatin induces an overproduction of reactive oxygen species and depletion of glutathione in endothelial cells,[29,30] which plays a pivotal role in SOS development.[31] DeLeve et al.[32] have also demonstrated that sinusoidal endothelial cell release of matrix metalloproteinase (MMP)-2 and MMP-9 precipitates the early steps of SOS by degrading the extracellular matrix in the spaces of Disse and endothelial cell degradation and embolization. VEGF is known to regulate MMP-9 activation by inducing its expression. In patients undergoing bone marrow transplantation, the serum VEGF level is found to be elevated in individuals who develop SOS, and the degree of the increase in VEGF serum level parallels the clinical severity of SOS.[33] Therefore, although the mechanisms that explain a bevacizumab-mediated decrease in the hepatic toxicity of oxaliplatin remain unknown, VEGF blockade may attenuate sinusoidal injury by down-regulating MMP-9 production.

The clinical relevance of sinusoidal dilation with respect to outcomes after hepatic resection is increasingly recognized. We reported no increase in morbidity after a median of 12 weeks of treatment with oxaliplatin-based chemotherapy,[4] but 2 recent studies have described an increase in blood transfusions and complications in patients treated preoperatively for >12 weeks.[11,12] In rare cases, prolonged treatment of CLM with oxaliplatin has been associated with SOS and death.[13] Although our study cannot clarify whether bevacizumab protects from long-term exposure to oxaliplatin, the protective effect of bevacizumab observed in the current study is attractive.

Although this study is limited by its retrospective nature, the increase in the magnitude of pathologic response after treatment with bevacizumab and the reduction in the incidence and severity of sinusoidal dilation strongly suggest a benefit for the use of bevacizumab-containing regimens over oxaliplatin alone. Further studies are needed to expand on these initial findings and to provide further insight into the role of bevacizumab as a potentially protective agent against the broader spectrum of diseases associated with SOS.

REFERENCES

1. Adam R, Delvart V, Pascal G, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. *Ann Surg*. 2004;240:644–657.
2. Alberts SR, Horvath WL, Sternfeld WC, et al. Oxaliplatin, fluorouracil, and leucovorin for patients with unresectable liver-only metastases from colorectal cancer: a North Central Cancer Treatment Group phase II study. *J Clin Oncol*. 2005;23:9243–9249.
3. Poston G, Adam R, Vauthey JN. Downstaging or downsizing: time for a new staging system in advanced colorectal cancer? *J Clin Oncol*. 2006;24:2702–2706.
4. Vauthey JN, Pawlik TM, Ribero D, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. *J Clin Oncol*. 2006;24:2065–2072.
5. Adam R, Pascal G, Castaing D, et al. Tumor progression while on chemotherapy: a contraindication to liver resection for multiple colorectal metastases? *Ann Surg*. 2004; 240:1052–1061.
6. Allen PJ, Kemeny N, Jarnagin W, DeMatteo R, Blumgart L, Fong Y. Importance of response to neoadjuvant chemotherapy in patients undergoing resection of synchronous colorectal liver metastases. *J Gastrointest Surg*. 2003;7:109–117.
7. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst*. 2000;92:205–216.
8. Grothey A, Hedrick EE, Mass RD, et al. Response rate using conventional criteria is a poor surrogate for clinical benefit on progression-free (PFS) and overall survival (OS) in metastatic colorectal cancer (mCRC): a comparative analysis of N9741 and AVF2107. *Proc Am Soc Clin Oncol*. 2006;24:150s.
9. Rubbia-Brandt L, Giostra E, Brezault C, et al. Importance of histological tumor response assessment in predicting the outcome in patients with colorectal liver metastases treated with neoadjuvant chemotherapy followed by liver surgery. *Ann Oncol*. 2007;18:299–304.
10. Malaisrie SC, Hofstetter WL, Correa AM, et al. The addition of induction chemotherapy to preoperative, concurrent chemoradiotherapy improves tumor response in patients with esophageal adenocarcinoma. *Cancer*. 2006;107:967–974.
11. Karoui M, Penna C, Amin-Hashem M, et al. Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. *Ann Surg*. 2006;243:1–7.
12. Aloia T, Sebagh M, Plasse M, et al. Liver histology and surgical outcomes after preoperative chemotherapy with fluorouracil plus oxaliplatin in colorectal cancer liver metastases. *J Clin Oncol*. 2006;24:4983–4990.
13. Tisman G, MacDonald D, Shindell N, et al. Oxaliplatin toxicity masquerading as recurrent colon cancer. *J Clin Oncol*. 2004;22:3202–3204.

14. Hochster HS, Hart LL, Ramanathan RK, Hainsworth JD, Hedrick EE, Childs BH. Safety and efficacy of oxaliplatin/fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer (mCRC): final analysis of the TREE-study. *Proc Am Soc Clin Oncol*. 2006:148s.
15. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med*. 2004;350:2335–2342.
16. Giantonio BJ, Catalano PJ, Meropol NJ, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX 4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. *J Clin Oncol*. 2007;12:1539–1544.
17. Ellis LM, Curley SA, Grothey A. Surgical resection after downsizing of colorectal liver metastasis in the era of bevacizumab. *J Clin Oncol*. 2005;23:4853–4855.
18. Rubbia-Brandt L, Audard V, Sartoretti P, et al. Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. *Ann Oncol*. 2004;15:460–466.
19. Ajani JA, Mansfield PF, Crane CH, et al. Paclitaxel-based chemoradiotherapy in localized gastric carcinoma: degree of pathologic response and not clinical parameters dictated patient outcome. *J Clin Oncol*. 2005;23:1237–1244.
20. Benoist S, Brouquet A, Penna C, et al. Complete response of colorectal liver metastases after chemotherapy: does it mean cure? *J Clin Oncol*. 2006;24:3939–3945.
21. Bechtold RE, Chen MY, Stanton CA, Savage PD, Levine EA. Cystic changes in hepatic and peritoneal metastases from gastrointestinal stromal tumors treated with Gleevec. *Abdom Imaging*. 2003;28:808–814.
22. Goh BK, Chow PK, Chuah KL, Yap WM, Wong WK. Pathologic, radiologic and PET scan response of gastrointestinal stromal tumors after neoadjuvant treatment with imatinib mesylate. *Eur J Surg Oncol*. 2006;32:961–963.
23. Bouzourene H, Bosman FT, Seelentag W, Matter M, Coucke P. Importance of tumor regression assessment in predicting the outcome in patients with locally advanced rectal carcinoma who are treated with preoperative radiotherapy. *Cancer*. 2002;94:1121–1130.
24. Willmot FC, Robertson GW. Senecio disease, or cirrhosis of the liver due to senecio poisoning. *Lancet*. 1920;196:848–849.
25. DeLeve LD, Shulman HM, McDonald GB. Toxic injury to hepatic sinusoids: sinusoidal obstruction syndrome (veno-occlusive disease). *Semin Liver Dis*. 2002;22:27–42.
26. Carreras E, Bertz H, Arcese W, et al. Incidence and outcome of hepatic veno-occlusive disease after blood or marrow transplantation: a prospective cohort study of the European Group for Blood and Marrow Transplantation. European Group for Blood and Marrow Transplantation Chronic Leukemia Working Party. *Blood*. 1998;92:3599–3604.
27. McDonald GB, Hinds MS, Fisher LD, et al. Veno-occlusive disease of the liver and multiorgan failure after bone marrow transplantation: a cohort study of 355 patients. *Ann Intern Med*. 1993;118:255–267.
28. Hasegawa S, Horibe K, Kawabe T, et al. Veno-occlusive disease of the liver after allogeneic bone marrow transplantation in children with hematologic malignancies: incidence, onset time and risk factors. *Bone Marrow Transplant*. 1998; 22:1191–1197.
29. Laurent A, Nicco C, Chereau C, et al. Controlling tumor growth by modulating endogenous production of reactive oxygen species. *Cancer Res*. 2005;65:948–956.
30. Alexandre J, Nicco C, Chereau C, et al. Improvement of the therapeutic index of anticancer drugs by the superoxide dismutase mimic mangafodipir. *J Natl Cancer Inst*. 2006;98: 236–244.
31. Wang X, Kanel GC, DeLeve LD. Support of sinusoidal endothelial cell glutathione prevents hepatic veno-occlusive disease in the rat. *Hepatology*. 2000;31:428–434.
32. Deleve LD, Wang X, Tsai J, Kanel G, Strasberg S, Tokes ZA. Sinusoidal obstruction syndrome (veno-occlusive disease) in the rat is prevented by matrix metalloproteinase inhibition. *Gastroenterology*. 2003;125:882–890.
33. Iguchi A, Kobayashi R, Yoshida M, et al. Vascular endothelial growth factor (VEGF) is 1 of the cytokines causative and predictive of hepatic veno-occlusive disease (VOD) in stem cell transplantation. *Bone Marrow Transplant*. 2001; 27:1173–1180.