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Chemotherapy with Bevacizumab Does Not Affect Liver Regeneration after Portal Vein Embolization in the Treatment of Colorectal Liver Metastases

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Abstract

Introduction—Blockage of vascular endothelial growth factor (VEGF) in murine models has been shown to impair liver regeneration after partial hepatectomy. The aim of this study was to evaluate the effects of chemotherapy with or without bevacizumab (monoclonal antibody anti-VEGF) on liver regeneration after portal vein embolization (PVE) in the treatment of colorectal liver metastases (CLM) and its possible effect on postoperative outcome after major liver resection.

Methods—Records of 65 consecutive patients treated with or without preoperative chemotherapy (+/– bevacizumab) and PVE for CLM from September 1995 to February 2007 were reviewed from a prospective database. Future liver remnant (FLR) volume, degree of FLR hypertrophy (DH) after PVE, morbidity, mortality, and survival were analyzed.

Results—Preoperative PVE was performed after chemotherapy in 43 patients and without chemotherapy in 22 patients. Among the 43 patients treated with chemotherapy, 26 received concurrent bevacizumab. After a median of 4 weeks after PVE, there was no difference in FLR volume increase among patients treated with or without chemotherapy. Similarly, there was no statistically significant difference in DH among patients treated without (mean 10.1%) or with chemotherapy, with or without bevacizumab (8.8% and 6.8%) ($p = 0.11$). Forty-eight of the 65 (74%) patients underwent extended right or right hepatectomy after PVE. No differences in morbidity and mortality were observed among patients treated with or without preoperative chemotherapy (+/– bevacizumab).

Conclusions—Preoperative chemotherapy with bevacizumab does not impair liver regeneration after PVE. Liver resection can be performed safely in patients treated with bevacizumab before PVE.

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Keywords

bevacizumab; preoperative chemotherapy; liver regeneration; liver resection; portal vein embolization; colorectal metastases

INTRODUCTION

Vascular endothelial growth factor (VEGF, also known as VEGF-A) plays a key role in tumor angiogenesis, growth, and hematogenous metastases by promoting endothelial cell proliferation, migration, and survival. It also increases vascular permeability, induces degradation of the basement membrane to allow endothelial cell migration and invasion, and is overexpressed in many solid tumors.^{1, 2} Bevacizumab is a humanized monoclonal antibody that targets VEGF and is the first angiogenesis inhibitor to have been approved by the U.S. Food and Drug Administration. In a phase 3 trial of patients with metastatic colorectal cancer, the addition of bevacizumab to standard chemotherapy resulted in improved overall and progression-free survival, resulting in its approval as first-line therapy for metastatic colorectal cancer.³

Despite the increasing use of bevacizumab, its effects on liver regeneration after hepatic resection have not been clarified. Angiogenesis plays a critical role in liver regeneration, as demonstrated by a rise in VEGF mRNA and protein levels after partial hepatectomy in animal models.⁴ In addition, blockage of VEGF in animals suppresses hepatic proliferation after partial hepatectomy.⁵ Portal vein embolization (PVE) has been shown to induce a regenerative response that mirrors the regeneration that occurs after partial hepatectomy. PVE induces atrophy of the embolized lobe (to be resected) with compensatory hypertrophy of the non-embolized lobe (the future liver remnant, FLR).^{6, 7} The degree of liver hypertrophy after PVE is accurately quantified with computed tomography (CT) liver volumetry.

The aim of this study was to evaluate the effects of chemotherapy with or without bevacizumab on liver regeneration after PVE in the treatment of colorectal liver metastases (CLM) by evaluating changes in the future liver remnant volume and degree of hypertrophy after PVE. A secondary aim was to assess the effects of pre-PVE neoadjuvant chemotherapy, with or without bevacizumab, on postoperative outcomes after major liver resection.

MATERIALS AND METHODS

From a prospective hepatobiliary database at the University of Texas M. D. Anderson Cancer Center, 65 consecutive patients who underwent PVE in anticipation of major liver resection for CLM were identified between September 1995 and April 2007. To differentiate the effects of cytotoxic chemotherapy independently from those of bevacizumab, patients were grouped as follows: (A) patients who received chemotherapy with bevacizumab before PVE, (B) patients who received chemotherapy without bevacizumab before PVE, and (C) patients who were not treated with chemotherapy before PVE. All patients in groups A and B received at least three cycles of neoadjuvant chemotherapy as first-line treatment. Patients who had undergone prior liver resection or received multiple lines of chemotherapy before

PVE were excluded. The study was conducted under an institutional review board-approved protocol.

PVE was performed as previously described^{8, 9} based on volumetry of the anticipated future liver remnant (FLR) after evaluation by the operating surgeon (E.K.A. or J.N.V.). PVE was indicated when the FLR volume was 20% of the estimated total liver volume (TLV) in patients with normal liver, 30% in patients with fibrosis or severe liver injury.^{10, 11} Embolization of segment 4 was performed when an extended right hepatectomy was planned on the basis of tumor location.

The FLR volume was measured directly using three-dimensional CT volumetry as described previously.^{12, 13} TLV was calculated from the patient's body surface area (BSA) using a mathematical formula ($TLV [cm^3] = -794.41 + 1267.28 \times BSA [m^2]$).^{14, 15} The ratio between FLR volume and TLV was defined as the standardized FLR (sFLR). The difference between the sFLR before and after PVE was defined as the degree of hypertrophy (DH). CT liver volumetry was performed before and a median of 4 weeks (range, 2-10 weeks) after PVE to assess changes in sFLR and DH.

Perioperative morbidity was reported according to the classification proposed by Dindo et al.¹⁶ Grade I and II complications were defined as minor, and grade III and IV complications as major. Postoperative mortality was defined as any death within 90 days after surgery or within the hospital stay during which the surgery was performed. Hepatic dysfunction was defined as a peak postoperative bilirubin level greater than 3 mg/dl (51.3 μ mol/L)¹⁷ or a prothrombin time longer than 18 seconds.¹⁸

Statistical analysis was performed with SPSS software (SPSS Inc., version 12, Chicago, IL). Continuous data were expressed as mean $\pm$ standard deviation (SD) (95% confidence interval [c.i.]) unless otherwise indicated and compared using the Mann-Whitney *U* test, the T-test, or the Kruskal-Wallis test, as appropriate. Dichotomous variables were compared by means of the χ^2 test or Fisher's exact test, as appropriate. The relationship between liver regeneration and clinical outcome was investigated using the sFLR after PVE and the DH. Statistical significance was defined as $P < 0.05$.

RESULTS

Clinicopathological features of the 65 patients studied are shown in Table 1. Oxaliplatin-based chemotherapy with bevacizumab was administered before PVE in 26 patients (group A) and without bevacizumab in 17 patients (group B, figure 1). Twenty-two patients underwent PVE without prior chemotherapy (group C). Group A patients received a median of 6 cycles of chemotherapy (range, 3-20), which was discontinued a median of 7.4 weeks (range, 2-35 weeks) before PVE. Group B patients received a median of 5 cycles of chemotherapy (range, 3-23), which was discontinued a median of 7.2 weeks (range, 2-20 weeks) before PVE. In group A patients, the last cycle of chemotherapy was usually given without bevacizumab; thus, the median time interval between the last dosage of bevacizumab and PVE was 7.9 weeks (range 3-36 weeks).

Regeneration after PVE (FLR and DH)

Liver volumetry data are shown in Table 2. The absolute FLR volume increased significantly after a median of 4 weeks (range, 2-10 weeks) after PVE in all groups. The gain in absolute FLR volume after PVE was neither affected by chemotherapy before PVE nor by the addition of bevacizumab ($P=0.35$, figure 2).

Similarly, neither chemotherapy nor bevacizumab affected the increase in sFLR after PVE ($P=0.56$). The sFLR in patients treated with bevacizumab (group A) increased from a mean of 21% to 30%. In patients who received chemotherapy without bevacizumab (group B), the sFLR increased from a mean of 22% to 28%. Patients who did not receive chemotherapy (group C) had an increase in mean sFLR from 22% to 32%.

There was no statistically significant difference in DH among the patient groups ($P=0.15$). The mean values of DH after PVE for groups A, B, and C were 9%, 7%, and 10%, respectively. The duration of pre-PVE chemotherapy did not affect liver regeneration, as there was no correlation between DH and number of cycles of pre-PVE chemotherapy, with or without bevacizumab ($P=0.75$). Figure 3 demonstrates an excellent hypertrophic response after PVE in a patient who received 11 cycles of chemotherapy with bevacizumab, with post-PVE sFLR of 42% and DH of 15%.

Resectability and outcome

A total of forty-eight of the 65 (74%) patients underwent extended right or right hepatectomy after PVE. Seventeen patients (26%) did not undergo hepatic resection after PVE because of extrahepatic (eight patients) or intrahepatic (two) progression of disease, inadequate hepatic regeneration (four) or significant medical co-morbidities (three). Among patients with inadequate hepatic regeneration after PVE, one had received preoperative chemotherapy with bevacizumab, two without bevacizumab, and one had received no chemotherapy. The surgical procedures performed are summarized in Table 3. Of note, 11 of 36 patients who underwent extended right hepatectomy and one of 12 who had right hepatectomy also had a synchronous extrahepatic procedure, including diaphragm resection, vena cava resection, common bile duct resection, lung wedge resection, and bowel resection.

After a median follow-up of 13 months, the median survival for the resected patients with or without chemotherapy was 35 versus 55 months, respectively ($p=0.2$). No statistically significant differences in postoperative hepatic dysfunction, morbidity, and mortality were observed among the patient groups. Median hospital stay after hepatic resection for all resected patients was 7 days (range, 5-52 days), no statistically significant difference between patients undergone chemotherapy with or without bevacizumab was observed (7 versus 8 days, respectively; $p=0.89$).

In the without chemotherapy group postoperative complications occurred in 8 patients (50%). Grade II complications in 5 patients included self-limited biliary fistula (two) and hepatic dysfunction (three), pneumonia (two). Two patients experienced grade IIIa complications, including bile leak/biloma (one), intra-abdominal fluid collection and hepatic dysfunction (one). One patient underwent reoperation for small bowel perforation (Grade IIIb complication). Mortality was nil in the without chemotherapy group.

In the chemotherapy group hepatic resection was performed in 32 patients (74%). (Table 3) Twenty-two extended right and ten right hepatectomies were performed. Postoperative complications occurred in 15 patients (47%). One patient experienced Grade I complication (elevated serum potassium level), Grade II complications in 4 patients included hepatic dysfunction (two), atrial fibrillation (one), and prolonged ileus (one). Eight patients experienced Grade IIIa complications, including hepatic dysfunction (two), hepatic insufficiency (three), and intra-abdominal fluid collection (three). Two patients died (90-day mortality) of hepatic insufficiency and multi-organ failure (Grade V). In summary a total of thirteen patients developed hepatic dysfunction, five of whom experienced hepatic insufficiency and two of these died from liver failure. (Table 3)

DISCUSSION

The addition of bevacizumab to standard chemotherapy has resulted in improved overall and progression-free survival rates in patients with metastatic colorectal cancer.³ However, the critical role of VEGF in liver regeneration has raised concerns regarding impaired liver regeneration after preoperative administration of bevacizumab. In this study, we analyzed the effects of bevacizumab and chemotherapy administered to patients before PVE in anticipation of major liver resection for CLM and found that chemotherapy with bevacizumab did not impair liver regeneration after PVE. We also found that the incidence of postoperative complications and 90-day mortality were not increased with the addition of bevacizumab to oxaliplatin-based chemotherapy. These findings support previous studies on the safety of bevacizumab before hepatectomy for CLM.¹⁹⁻²¹

To our knowledge, this is the first study to analyze the effects of bevacizumab on liver regeneration in humans. Preclinical data in animal models are lacking because bevacizumab specifically recognizes the human form of VEGF, and not murine VEGF. However, animal studies have demonstrated that liver regeneration depends upon VEGF and angiogenesis.²² In rats, exogenous VEGF after partial hepatectomy stimulates liver regeneration by inducing proliferation of hepatocytes and liver sinusoidal endothelial cells, while anti-VEGF therapy suppresses hepatic proliferation. In the current study, the hypertrophy of the FLR after PVE was not affected by bevacizumab. The likely explanation for the discrepancy between our clinical study and previous animal studies is the timing of bevacizumab administration. In murine models, angiogenesis and hepatocyte proliferation were delayed when anti-VEGF was administered 0-96 hours after partial hepatectomy. In the present report, patients underwent PVE a median of 8 weeks after the last dose of bevacizumab. A shorter time interval between bevacizumab administration and PVE could interfere with angiogenesis and liver regeneration. This study supports the recommendation to stop bevacizumab 6-8 weeks before any intervention that causes insult to the liver, such as PVE or hepatic resection.^{19, 23}

We chose to study the effects of bevacizumab on liver regeneration in patients who underwent PVE before major liver resection because they represent a relatively uniform group of patients who have not undergone previous liver resection. In addition, they underwent systematic analysis of liver volumes before and after PVE to assess changes in sFLR and DH. PVE has been shown to mimic the effects of liver regeneration after resection.^{6, 7} PVE results in apoptosis in the embolized lobes with compensatory

proliferation of the non-embolized lobe. In a rat model of portal vein ligation, the ligated lobes atrophied to 10% of their original weight within two weeks, while the nonoccluded lobes hypertrophied to reconstitute the original liver mass.⁶

In patients with CLM, PVE is frequently part of a multimodal treatment that includes preoperative chemotherapy. In this study, we found that treatment with chemotherapy, with or without bevacizumab, did not affect the gains in sFLR, which ranged from a mean of 21%–22% before PVE to 28%–32% after PVE. Previously, we showed that in patients without underlying liver disease, the minimum sFLR for safe major hepatectomy was 20%. In addition, a DH of at least 5% has been shown to be predictive of a decreased risk of postoperative hepatic dysfunction.²⁴ In this series, the mean DH ranged from 7%–10% and was not affected by treatment with chemotherapy or bevacizumab. The rate of postoperative hepatic dysfunction was similar among patient groups and ranged between 25%–31%.

The second major finding of this study was that postoperative morbidity and mortality rates were not higher in patients treated with chemotherapy, with or without bevacizumab. This is in agreement with previous studies showing that perioperative treatment with bevacizumab does not increase morbidity after hepatectomy for CLM.^{19, 21} However, large randomized trials on bevacizumab for stage IV colorectal cancer have demonstrated rare but potentially fatal risks of gastrointestinal perforation and arterial thrombotic events when surgery was performed while patients were on bevacizumab treatment. In a pooled analysis, wound healing complications after major surgery occurred in 13% of bevacizumab-treated patients, compared with 3.4% of control patients.²⁵ These data highlight the importance of stopping bevacizumab 6–8 weeks before performing elective hepatic resection or PVE.

In this series, patients received oxaliplatin-based chemotherapy without increase in postoperative morbidity and mortality, as previously shown in a large, multi-institutional study.²⁶ However, oxaliplatin has been associated with hepatic sinusoidal dilatation^{26, 27} In a previous clinical study, we showed that bevacizumab reduces the incidence and severity of oxaliplatin-related hepatic sinusoidal dilation;²⁰ this finding suggests a benefit for the use of bevacizumab-containing regimens over oxaliplatin alone. The current study demonstrates that the addition of bevacizumab to oxaliplatin-based chemotherapy does not worsen outcomes after hepatectomy. In fact, by reducing sinusoidal liver injury, bevacizumab may promote liver regeneration, which might otherwise be impaired by hepatic sinusoidal dilation.

In addition, the duration of pre-PVE chemotherapy did not affect liver regeneration and postoperative outcome in the present study. This is in contrast with previous studies showing higher postoperative complication rates related to the duration of chemotherapy Karoui et al.²⁸ reported a significant higher morbidity among patients who received 6 cycles compared with < 6 cycles. Similarly, in the study by Aloia et al.,²⁹ patients who received > 12 courses of chemotherapy (5-FU ± oxaliplatin) were significantly predisposed to reoperation and longer hospitalization than patients who received 12 courses. In the current study, for instance, one patient had a great hypertrophy (DH: 15%) and an uneventful postoperative recovery, in spite of prolonged chemotherapy with 11 cycles including bevacizumab (Figure

3). Our results likely did not show a correlation between duration of preoperative chemotherapy and postoperative outcome because of the small number of patients.

In conclusion, neoadjuvant chemotherapy with bevacizumab does not impair the liver regeneration after PVE and allows an adequate hypertrophy of the FLR. Patients with CLM can safely undergo chemotherapy with bevacizumab and PVE before liver resection.

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SYNOPSIS

The study evaluates the effects of chemotherapy with or without bevacizumab on liver regeneration after PVE in 65 patients treated for colorectal liver metastases. The hypertrophy of the FLR following PVE was not affected by the addition of bevacizumab to the pre-PVE chemotherapy regimen.

Figure 1.
Flowchart showing patients grouped by treatment before PVE.

Figure 2. Changes in absolute future liver remnant volume after PVE in patients without chemotherapy (red line, full line), and with chemotherapy with bevacizumab (blue line, dot line), and without bevacizumab (black line, dash line), $P=0.35$. Values are mean $\pm$ standard deviation.

Figure 3.

A 62-year-old male patient with CLM received 11 cycles of chemotherapy with oxaliplatin and bevacizumab before right PVE.

A. CT of the liver before right PVE shows a sFLR volume (segments 2,3, and 4) of 26%.

B. CT of the liver 3.3 weeks after right PVE shows increased sFLR volume to 42% with a degree of hypertrophy of 15%.

Table 1

Patients characteristics

	Chemotherapy with bevacizumab, group A	Chemotherapy without bevacizumab, group B	No Chemotherapy group C
Number of patients	26	17	22
Sex ratio (M : F)	18 : 8	13 : 4	16 : 6
Mean (range) age (years)	57 ((36–68)	58 ((42–77)	58 ((37–76)
Diabetes mellitus			
Yes	6 ((23)	7 ((41)	6 (27)
No	20 ((77)	10 ((59)	16 ((73)
Body mass index (kg/m ²)			
Mean (range)	27.6 (19.3–48.4)	28 ((19.8–37.8)	28.1 (19.4–34)
< 25 kg/m ²	4 ((15)	6 ((35)	5 ((23)
25 kg/m ²	22 ((85)	11 ((65)	15 ((68)
Not available	–	–	2 ((9)
Non-tumorous liver			
No pathological changes	19 ((73)	11 ((65)	16 ((73)
Steatosis >30% or steatohepatitis *	1 ((4)	–	1 ((4)
Fibrosis (F1–4 [†])	6 ((23)	6 ((35)	5 ((23)
Severe fibrosis/cirrhosis (F5–6 [†])	–	–	–
Portal vein embolization			
Right PVE + 4	21 ((81)	12 ((71)	17 ((77)
Right PVE	5 ((19)	5 ((29)	4 ((18)
Left PVE	–	–	1 ((4)
Median weeks of interval between chemotherapy and PVE (range)	7.4 (2–35)	7.2 (2–20)	–
Median number of cycles of chemotherapy (range)	6 ((3–20)	5 ((3–23)	–

All differences among groups were non-significant.

Values in parentheses are percentages unless indicated otherwise.

* Kleiner score 4 or more³¹.

[†] Fibrosis score according to Ishak *et al.*³². Right PVE + 4 = right portal vein embolization (PVE) extended to segment 4 portal branches.

Table 2

Liver volumetry

	Chemotherapy with bevacizumab, group A	Chemotherapy without bevacizumab, group B	Number chemotherapy, group C
Number of patients	26	17	22
FLR volume pre PVE (cc)			
Mean	376.6	382.7	373.2
95% CI	293.7-459.4	280.9-484.4	266.4-479.9
SD	200.8	197.9	234.4
FLR volume post PVE (cc)			
Mean	537.4	491.9	547.9
95% CI	433.7-640.9	379.5-604.5	418.7-677
SD	251	211.2	283.7
sFLR volume pre PVE (%)			
Mean	20.7	21.8	21.6
95% CI	16.9-24.4	16-27.6	16.3-26.9
SD	9.1	11.3	11.6
sFLR volume post PVE (%)			
Mean	29.5	28.4	31.7
95% CI	25-34	21.8-34.8	25.5-37.9
SD	10.9	12.1	13.5
DH (%)			
Mean	8.8	6.8	10.1
95% CI	6.7-11.	5.2-8.4	7.6-12.6
SD	5.3	2.9	5.6

All differences among groups were non-significant.

FLR = future liver remnant volume. pre PVE = before PVE. CI= Confidence Interval. SD = standard deviation. post PVE = after PVE. sFLR = standard FLR. DH = degree of hypertrophy.

Table 3

Surgical procedures and postoperative complications in 48 patients who had hepatic resection

	Chemotherapy with bevacizumab, group A	Chemotherapy without bevacizumab, group B	No chemotherapy, group C	Total number of patients
Number of patients who underwent resection	19	13	16	48
Resectability (%)	73	76	73	74
Procedures				
Extended right hepatectomy	12 (63)	10 (77)	14 (87.5)	36 (75)
Right hepatectomy	7 (37)	3 (23)	1 (6.3)	11 (23)
Left hepatectomy			1 (6.3)	1 (2)
Extrahepatic				
Diaphragm resection	1	3	2 *	6
CBD resection	–	1	1 *	2
Bowel resection	–	–	1	1
Lung resection	1	1	–	2
IVC resection	–	–	2	2
Postoperative complications	8 (42)	7 (54)	8 (50)	23 (48)
Minor (grade I–II)	4 (21)	1 (8)	5 (31)	10 (21)
Major (grade III–IV)	3 (16)	5 (38)	3 (19)	11 (23)
Hepatic dysfunction	5 (26)	4 (31)	4 (25)	13 (27)
Death within 90 days	1 (5)	1 (8)	0	2 (4)

* One patient underwent two extrahepatic procedures.

All differences among groups were non-significant. Values in parentheses are percentages. Complications were graded according to the classification of Dindo *et al.* {Dindo, 2004 #2194}.

CBD = common bile duct, IVC = inferior vena cava.