ORIGINAL ARTICLE

Perioperative chemotherapy with bevacizumab and liver resection for colorectal cancer liver metastasis

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Abstract

Background: Surgery remains the only curative option for patients with colorectal cancer liver metastases (CRLM). Perioperative chemotherapeutic strategies have become increasingly popular in the treatment of CRLM. Although the role of bevacizumab (Bev) in this setting remains unclear, its widespread use has raised concerns about the use of Bev as part of perioperative chemotherapy.

Methods: We retrospectively reviewed all patients who received Bev and underwent liver resection between July 2004 and July 2008 at the McGill University Health Center. Chemotherapy-related toxicity, response to chemotherapy, surgical morbidity and mortality, liver function and survival data were assessed.

Results: A total of 35 patients were identified. Of these, 26 (74.3%) patients received oxaliplatin-based cytotoxic chemotherapy, six (17.1%) received irinotecan-based therapy and the remainder received both agents. A total of 17 patients (48.6%) underwent portal vein embolization prior to resection and 12 (34.3%) underwent staged resection for extensive bilobar disease. A median of six cycles of preoperative Bev were administered. Nine patients (25.7%) experienced grade 3 or higher chemotherapy-related toxicities. Four events were deemed to be related to Bev. The overall response rate was 65.7% (complete and partial response). One patient progressed on therapy, but this did not prevent R0 resection. The incidence of postoperative morbidity was 42.3%. A total of 21.7% of complications were Clavien grade 3 or higher. There were no perioperative mortalities. There were no cases of severe sinusoidal injury or steatohepatitis. The Kaplan–Meier estimate of 4-year survival was 52.5%.

Conclusions: These data confirm the safety of chemotherapy regimens which include Bev in the perioperative setting and demonstrate that such perioperative chemotherapy in patients with CRLM does not adversely affect patient outcome. There was no increase in perioperative morbidity compared with published rates. The addition of Bev to standard chemotherapy may improve response rates, which may, in turn, impact favourably on patient survival.

Keywords
bevacizumab, peri-operative chemotherapy, colon cancer liver metastasis, liver resection

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Introduction

Colorectal cancer is the third most common cancer in North America, and is the third leading cause of cancer-related death. The American Cancer Society estimates that about 108 070 new cases of colon cancer and 40 740 new cases of rectal cancer will have emerged in 2008 in the USA. Combined, these will cause about 49 960 deaths.1 Approximately 50% of patients will be diagnosed with colorectal cancer liver metastasis (CRLM) during the course of their disease.2 Around 20–25% of patients will have synchronous liver metastases (LM) at presentation3 and a further 20–25% will develop metachronous LMs at a later date.
Surgical resection remains the only curative therapy for patients with CRLM. The most recently published series have seen the 5-year survival rate rise beyond 60%.

In the current study, we review the perioperative use of bevacizumab (Bev) Avastin™; Hoffmann-La Roche, Basel, Switzerland), a humanized monoclonal antibody that targets vascular endothelial growth factor (VEGF), remains controversial. Although the survival benefit of Bev used in the palliative setting has been established, its impact on response rate is not as clear as recent data from the NO16966 trial failed to show an increased response rate when Bev was combined with FOLFOX-4. Despite this, Bev is commonly used in combination with cytotoxic chemotherapy before surgical resection in patients with CRLM. Because of reports of haematologic toxicity, intestinal perforation and an increased risk of postoperative bleeding, surgeons and oncologists have been reluctant to use Bev in the perioperative setting. However, a retrospective study from the MD Anderson Cancer Center showed no significant increase in hepatoportal or wound complications, and no postoperative deaths in patients who received preoperative Bev. In the same series, only 12% of patients experienced preoperative adverse events related to Bev therapy. Other series have also confirmed that the neoadjuvant use of Bev in combination with cytotoxic agents did not significantly increase postoperative complications.

In the current study, we review our experience with a Bev and oxaliplatin-based chemotherapy regimen administered to patients with CRLM perioperatively in order to determine the safety and efficacy of this regimen and its impact on survival.

Materials and methods

This retrospective review was authorized according to institutional protocol by the Director of Professional Services at McGill University Health Centre. Patients who had undergone liver resection between July 2004 and July 2008 at the McGill University Health Centre and who had received Bev in the perioperative period were identified through the hepatopancreatobiliary (HPB) database. All patients who received Bev and underwent liver resection for CRLM were included.

A total of 45 patients who had received Bev combined with cytotoxic chemotherapy were identified. Of these, 10 had received Bev only in the adjuvant setting for recurrent disease. The remaining 35 are the focus of this analysis. Basic demographic data, disease-specific data, information on the chemotherapy regimens administered, chemotherapy-related toxicities, perioperative data, imaging data, pathology reports and survival data were collected and reviewed. Postoperative complications were reviewed and graded according to the Clavien classification system. The primary objective of the study was to examine the effect of the addition of Bev on treatment-related toxicity and perioperative morbidity. Secondary outcomes included response to therapy as determined by Response Evaluation Criteria in Solid Tumours (RECIST) criteria and the effect of this therapy on overall patient survival.

Although the actual chemotherapy regimen to be used on a patient was decided at the discretion of the treating oncologist, the decision was guided by HPB Tumor Board recommendations.

The strategy generally employed comprised 12 cycles of chemotherapy, of which six were administered preoperatively and six postoperatively. A break of 6–8 weeks between the last dose of Bev and surgery was targeted. Staged resections and portal vein embolization (PVE) were used liberally in this patient group. Response to treatment and resectability were assessed at a weekly multidisciplinary HPB Tumor Board meeting.

All patients underwent full preoperative assessment including liver function tests and cross-sectional imaging with computed tomography (CT), magnetic resonance imaging (MRI) and CT-positron emission tomography (PET) as indicated. All CTs and CT-PETs were reviewed by a radiologist. A RECIST classification was used to assess treatment response. In addition, degree of liver steatohepatitis and fibrosis staging scores were reviewed on pathology specimens as per Kleiner et al. Finally, liver dysfunction was defined for every patient post-surgery intervention using the scoring system established by Schindl et al. This scoring system is based on the peak bilirubin, international normalized ratio (INR), lactic acid and presence of encephalopathy, and has been correlated with clinical outcomes and measures of hepatic synthetic function (indocyanine green clearance).
Data were analysed using spss 17.0 (SPSS, Inc., Chicago, IL, USA) and stata 9.2 (StataCorp LP, College Station, TX, USA) was used for Kaplan–Meier estimation of survival.

Results
Overview
A total of 35 patients who received perioperative Bev with cytotoxic chemotherapy and underwent liver resection for CRLM were identified. Their median age was 57 years (range 41–78 years); 24 (68.6%) patients were male (Table 1). The colon was the primary site in 31 patients (88.6%). All patients were Eastern Cooperative Oncology Group (ECOG) status 2 or lower. The median number of lesions per patient was three (range 1–13). Twelve patients (34.3%) underwent staged resections for major bilobar disease involvement. Seventeen patients (48.6%) underwent PVE prior to resection.

In all, 26 (74.3%) patients received oxaliplatin-based cytotoxic chemotherapy. Six (17.1%) patients received irinotecan-based therapy and the remainder received both perioperatively. A median of six (range 4–16) cycles of Bev were administered preoperatively and a median of six (range 0–12) cycles were given postoperatively. The median delay between the last dose of Bev and surgery was 8 weeks (range 6–14 weeks).

Chemotherapy-related toxicity
Chemotherapy-related toxicities occurred in approximately two-thirds of patients (Table 2). Thirteen (37.1%) patients had no significant toxicity related to chemotherapy. Nine patients (25.7%) had toxicities of grade 3 or higher. Three (8.6%) patients experienced grade 4 toxicities, all of which were gastrointestinal in origin. Only four toxicity events were deemed to be directly related to Bev; these concerned one patient who developed an anaphylactic reaction, two patients with hypertension, and one patient with a significant episode of epistaxis. There were no arterial thromboembolic events or gastrointestinal perforations.

Response to chemotherapy
Response rate was assessed according to RECIST criteria (Table 3). The overall response rate was 65.7% (complete response and partial response). A total of 21 patients (31.4%) achieved stable disease. Only one patient progressed while on preoperative chemotherapy, but this did not prevent an R0 resection.

Perioperative data
A total of 35 patients underwent 41 hepatectomies. Overall, 22 right hepatectomies, seven left hepatectomies, seven left lateral sectionectomies, two extended right hepatectomies and three segmental resections were performed. The median blood loss was 1100 ml (range 200–4000 ml). Mean duration of surgery was 185 min (range 95–350 min). The majority of patients (70.7%) did not require intraoperative transfusion.

Postoperative complications
There were no perioperative mortalities in this series. The overall incidence of morbidity was 42.3% (Table 4). A total of 23 complications occurred in 15 patients. Of these, only five (21.7%) were grade 3 or higher according to the Clavien system. Ten patients experienced 13 infectious complications (five urinary tract infections, four wound infections, one episode of Clostridium difficile diarrhoea, one central line infection, one pneumonia and one intra-abdominal abscess). Two patients had bile leaks, and one

Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age, years (range)</td>
<td>57 (41–78)</td>
</tr>
<tr>
<td>Gender, M/F, n</td>
<td>24/11</td>
</tr>
<tr>
<td>Primary site</td>
<td></td>
</tr>
<tr>
<td>Colon, n (%)</td>
<td>31 (88.6%)</td>
</tr>
<tr>
<td>Rectum, n (%)</td>
<td>4 (11.4%)</td>
</tr>
<tr>
<td>Lesions, median (range)</td>
<td>3 (1–13)</td>
</tr>
<tr>
<td>Resections</td>
<td></td>
</tr>
<tr>
<td>Single, n</td>
<td>23</td>
</tr>
<tr>
<td>Staged, n</td>
<td>12</td>
</tr>
<tr>
<td>Portal vein embolization, n (%)</td>
<td>17 (48.6%)</td>
</tr>
<tr>
<td>CTX regimen</td>
<td></td>
</tr>
<tr>
<td>CPT-11, n (%)</td>
<td>6 (19.4%)</td>
</tr>
<tr>
<td>Oxaliplatin, n (%)</td>
<td>26 (72.2%)</td>
</tr>
<tr>
<td>Both, n (%)</td>
<td>3 (8.3%)</td>
</tr>
<tr>
<td>Median cycles BV</td>
<td></td>
</tr>
<tr>
<td>Preoperative, n (range)</td>
<td>6 (4–16)</td>
</tr>
<tr>
<td>Postoperative, n (range)</td>
<td>6 (0–12)</td>
</tr>
<tr>
<td>Time from last Bev to surgery, weeks (range)</td>
<td>8 (6–14)</td>
</tr>
<tr>
<td>Median follow-up, years (range)</td>
<td>2.9 (1–6)</td>
</tr>
</tbody>
</table>

Table 2 Chemotherapy-related toxicity

<table>
<thead>
<tr>
<th>Grade</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>13 (37.1%)</td>
</tr>
<tr>
<td>1</td>
<td>9 (25.7%)</td>
</tr>
<tr>
<td>2</td>
<td>4 (11.4%)</td>
</tr>
<tr>
<td>3</td>
<td>6 (17.1%)</td>
</tr>
<tr>
<td>4</td>
<td>3 (8.6%)</td>
</tr>
</tbody>
</table>

Table 3 Response to chemotherapy

<table>
<thead>
<tr>
<th>Response by RECIST</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive disease</td>
<td>1 (2.9%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>11 (31.4%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>21 (60.0%)</td>
</tr>
<tr>
<td>Complete response</td>
<td>2 (5.7%)</td>
</tr>
</tbody>
</table>

RECIST, Response Evaluation Criteria in Solid Tumours
required intervention by endoscopic retrograde cholangiopancreatography (ERCP). The second patient required revision of hepaticojejunostomy 3 months after the initial surgery. One patient had a perioperative myocardial infarction requiring angioplasty and stenting during the same admission. There was one anastomotic dehiscence in the only patient who underwent a closure of ileostomy at the same time as his liver resection; this required a second surgical intervention. One patient had a small bowel obstruction which resolved with conservative management. The average liver function score as per Schindl et al.\(^{23}\) was 3 (moderate dysfunction). Only two patients developed severe liver dysfunction. In one case, the patient developed grade 3 hepatic encephalopathy after the second resection of a staged procedure. In addition, he developed jaundice (peak bilirubin 80 µmol/l), elevation of INR (peak 1.7) and elevation of lactic acid (peak 4.2). These returned to normal by postoperative day 7. In the second case, after an extended left hepatectomy, the patient developed jaundice (peak bilirubin 83.5 µmol/l), elevation of INR (peak 1.8), and elevated lactic acid (peak 3.6). She developed a late leak from her hepaticojejunostomy, which was revised 3 months after the original surgery.

**Chemotherapy-associated toxicity**
Twenty-four patients (68%) demonstrated some degree of steatosis in the resection specimens, of which six cases (17.1%) were moderate. Only four patients (11.4%) had steatohepatitis in the resected liver (three mild, one moderate) and there were no cases of severe steatohepatitis. No specimen demonstrated significant sinusoidal injury.

**Survival**
The median follow-up for this group of patients is 2.9 years. The Kaplan–Meier calculated 4-year survival is 52.5%. Median survival has not yet been reached (Fig. 1).

**Discussion**
The frequency of perioperative treatment strategies in the treatment of CRLM continues to increase despite a relative lack of prospective data to support their use. Proponents of these strategies cite the opportunity to downsize tumours and in some cases render unresectable tumours resectable, as well as the opportunity to identify non-responders to chemotherapy who are unlikely to benefit from surgical resection. Even among those who espouse the use of perioperative chemotherapy, there has been reluctance to add antiangiogenic agents for fear of increasing perioperative morbidity and mortality, especially when the primary tumour has not yet been resected. Certainly, there are reports of increased bleeding, delayed wound healing and even intestinal perforation associated with the use of Bev.\(^{25}\)

The concerns about increased perioperative complications are not limited to the antiangiogenic agents alone, as the occurrence of steatosis and steatohepatitis, and sinusoidal injury related to irinotecan and oxaliplatin, respectively, is now well characterized.\(^{11,26}\) Initial data also pointed to increased mortality associated with steatohepatitis,\(^{27}\) although this has not been reported in all series.\(^{28}\) Clearly even proponents of perioperative chemotherapy agree that it is vital to limit preoperative exposure to chemotherapy. The EPOC trial was designed with this in mind, limiting preoperative chemotherapy to only six cycles. At this exposure, the occurrence of sinusoidal injury has been shown to be low.\(^{29}\) Although the trial was negative for its primary endpoint, progression-free survival was increased in the patients who underwent perioperative chemotherapy and liver resection. This trial has provided the strongest evidence to date of the benefits of perioperative chemotherapy.

Several studies have examined the pathologic response of CRLM to preoperative chemotherapy. Znajda et al.\(^{30}\) evaluated a series of resection specimens, and developed a classification for these designated ‘remnants of uncertain malignant potential’.\(^{13}\) More recently, the MD Anderson group has proposed response to chemotherapy as a significant prognostic indicator in patients undergoing liver resection for CRLM.\(^{13}\) If response to preoperative chemotherapy is indeed a prognostic factor, then it follows that improving response to preoperative therapy should also improve patient prognoses. It is clear that there is an increase in response rate when Bev is added to cytotoxic therapy.\(^{14}\)

The present series reports on a cohort of 35 patients with CRLM who underwent liver resection and received perioperative Bev and cytotoxic chemotherapy. The incidence and severity of toxicity caused by the chemotherapy were low in this series (only three patients with grade 4 events), in keeping with previous reports.\(^{31}\) Only four toxicity events were attributable to Bev.
Perioperative morbidity occurred in 42.3% of patients, in keeping with recent reports from MD Anderson and Memorial Sloan Kettering Cancer Center (MSKCC).14,17 There were no mortalities. Because of concerns about wound healing after exposure to Bev, it is our strict policy to wait at least 6 weeks from the last dose of Bev to perform surgery. On a cautionary note, when bowel anastomosis and liver resection were combined, the patient suffered an anastomotic dehiscence.

This is the first series to report on the use of perioperative Bev in patients undergoing staged resection. In the 12 patients who underwent staged resections, there was no increase in perioperative morbidity, length of stay or severity of liver dysfunction after the second resection. Bev was avoided between the staged procedures. In addition, 18 patients in this series underwent PVE. There were no complications as a result of the procedure and adequate hypertrophy of the future liver remnant occurred in all cases.

The overall response rate to preoperative chemotherapy including Bev was 65.7%. This is among the highest response rates reported in the surgical literature. Only one patient had progressive disease and this did not prevent R0 resection. In addition, this is one of the first surgical series to report survival rates of patients with advanced CRLM undergoing perioperative chemotherapy including Bev. With a median follow-up of 2.9 years, the 4-year survival is 52.5%. Both the survival and response rates are particularly promising given that the patients included in this analysis received Bev before it became widely available at our institution. These patients therefore represent a subgroup of patients who were considered to have worse prognoses and were thus prescribed Bev.

**Conclusions**

In summary, these data demonstrate that the use of perioperative chemotherapy containing Bev in patients with CRLM does not adversely affect patient outcomes. There was no increase in perioperative morbidity and zero mortality. This compares favourably with published results. These data confirm the safety of chemotherapy regimens including Bev used in the perioperative setting. The addition of Bev to standard chemotherapy may improve response rates and, in the light of recently published data, this may, in turn, impact favourably on patient survival.

**Conflicts of interest**

None declared.

**References**


