Pre-operative Targeted Therapies in Patients with Hepatic Colorectal Cancer Metastases—Bevacizumab versus Cetuximab

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Abstract

Complete resection offers the greatest chance of cure for patients with isolated colorectal cancer liver metastases. While few patients present as candidates for curative surgery, induction chemotherapy may make patients with initially unresectable disease amenable to surgery. Even those whose disease is potentially curable at presentation may benefit from pre-operative neoadjuvant systemic therapy, particularly those deemed at high risk for relapse. Biological targeted therapies such as bevacizumab and cetuximab improve on standard systemic chemotherapeutic regimens in incurable patients; the rationale for their pre-operative use is also strong. Uncertainties remain as to which (if either) agent to preferentially use and their ultimate role in this setting must be better defined. This article reviews the concepts behind, and current data on, the use of pre-operative cetuximab and bevacizumab in patients with hepatic colorectal cancer metastases.

Keywords

Metastatic colorectal cancer, cetuximab, bevacizumab, hepatic metastases resection, pre-operative therapy, targeted therapy, biological agents, metastasectomy

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The liver is the most common site of metastases for patients with metastatic colorectal cancer (mCRC). In spite of the striking advances that have been made in the systemic treatment of mCRC, chemotherapy alone is rarely associated with long-term survival. Complete resection offers the greatest likelihood of prolonged survival for patients with isolated liver metastases from CRC; indeed, a review of data from the Memorial Sloan-Kettering Cancer Center suggests that the actual cure rate is at least 17% and potentially as high as 25%.[1]

Unfortunately, fewer than 20% of patients present as candidates for potentially curative surgery. Induction chemotherapy (so-called 'conversion' therapy) may, however, make patients with initially unresectable disease amenable to surgery.[2] Additionally, even those whose disease is potentially curable at presentation may benefit from neoadjuvant chemotherapy, particularly those deemed at higher risk for relapse by virtue of synchronous primary cancer and metastases, nodal involvement of the primary cancer, or multiple metastases.

Recent data suggest that the peri-operative addition of oxaliplatin, folinic acid (leucovorin), and fluorouracil (5-FU) (FOLFOX4) chemotherapy to surgery significantly improves three-year progression-free survival (PFS) for patients with resected liver metastases.[3] Biologically targeted therapies such as bevacizumab and cetuximab improve the efficacy of standard systemic chemotherapeutic regimens in incurable patients; the rationale for their potential pre-operative use is also strong. Their single-agent activity and toxicity profiles differ markedly, however, and no clear guidelines exist mandating the preferential use of one or the other.

Goals of Pre-operative Therapy

Conversion therapy is administered with the primary goal of downsizing a tumor to enable inoperable cancers to become resectable, or to make borderline resectable cancers removable with less major morbidity or with a greater chance of sparing normal organ tissue or function. True neoadjuvant therapy is treatment given to patients whose disease is already potentially resectable. It immediately addresses the micrometastatic burden outside the surgical field, at least theoretically, increasing potential cure rates.

As with conversion therapy, downsizing tumors and making resection easier may remain major goals; neoadjuvant treatment may be used to identify response markers to be utilized later in the course of treatment. Importantly, patients progressing under neoadjuvant chemotherapy have a similar prognosis to patients who do not undergo resection,[4] although it is unlikely that this alone would be a factor in deciding to avoid surgery.

Description of Agents

Bavacizumab

Bevacizumab is a monoclonal antibody directed against vascular endothelial growth factor (VEGF), an important mediator of angiogenesis. While bevacizumab has little or no single-agent activity in mCRC,[5] adding it to chemotherapy regimens containing fluoropyrimidines (5-FU and capecitabine) and irinotecan or oxaliplatin improves outcomes for patients with advanced disease. For example, Hurwitz and colleagues demonstrated that the addition of bevacizumab to bolus 5-FU/leucovorin plus irinotecan in first-line therapy resulted in an improvement in[6] the objective response rate (RR: 44.8 versus 34.8%), time to tumor progression (10.6 versus 6.2 months), and overall survival (OS: 20.3 versus 15.6 months).

The benefit of adding bevacizumab to oxaliplatin-containing chemotherapy appears to be more modest. In the NO16966 trial by Saltz and Cassidy,[7] the addition of bevacizumab to FOLFOX4 or capecitabine plus oxaliplatin (XELOX) resulted in an increase in PFS of 1.4 months. The superiority of bevacizumab was, however, only statistically evident in the XELOX subgroup (p=0.0026). Additionally, the OS difference did not reach statistical difference (21.3 versus 19.9 months) and the RR was similar in both groups (47 versus 49%).

Importantly, no evidence exists supporting the use of bevacizumab for the treatment of micrometastatic disease. Major advanced disease trials that have evaluated the efficacy of bevacizumab required measurable tumors. Also, bevacizumab does not appear to work in the adjuvant setting, where the potential metastatic burden is particularly low. The NSABP C-08 phase III trial compared 12 cycles of post-operative adjuvant FOLFOX6 alone versus 12 cycles of FOLFOX6 plus bevacizumab followed by an additional six months of bevacizumab in resectable, curable, non-metastatic CRC patients. It failed to show any improvement in OS or disease-free survival.[8]

Cetuximab

Cetuximab is a monoclonal antibody directed against the epidermal growth factor receptor (EGFR). EGFR activation and subsequent induction of its downstream pathways are important mediators of neoplastic cellular proliferation, differentiation and survival.

Cetuximab certainly has single-agent efficacy in mCRC, but only among patients whose tumors harbor no mutation in the *KRAS* gene. For example, analysis of the phase III CO.17 trial[9] (cetuximab versus best supportive care for patients with mCRC for whom no standard chemotherapy was available) demonstrated that cetuximab induced a 12.8% response rate in patients with wild-type *KRAS* tumors, but only 1.2% of patients with a mutated *KRAS* tumor had a response. Additionally, two front-line randomized mCRC studies showed an increase in overall RR with the addition of cetuximab to irinotecan- or oxaliplatin-based chemotherapy.[10,11] Additionally, two front-line randomized mCRC studies showed an increase in overall RR with the addition of cetuximab to irinotecan-or oxaliplatin-based chemotherapy. The benefits were, however, also restricted to patients with tumors with wild-type KRAS. In the phase III CRYSTAL trial,[10] the overall RR in the group receiving cetuximab–FOLFIRI (folinic acid, 5-FU and irinotecan) was significantly higher than those receiving FOLFIRI alone (46.9 versus 38.7%). In patients with wild-type *KRAS*, the RR rose to 59.3% for the cetuximab–FOLFIRI arm versus 43.2% for the FOLFIRI-alone arm. By contrast, in patients with mutated *KRAS* tumors the RR was 36.2% in the cetuximab–FOLFIRI group and 40.2% in the FOLFIRI-alone group.

Table 1: Comparison of Different First-line Chemotherapy Regimens in Terms of Response Rates and R0 Resection Rates

First-line Agents	Trial	RR (%)	R0 Resection Rates (%)
FOLFOX4/cetuximab	OPUS[11]	61*	9.8*
FOLFIRI/cetuximab	CRYSTAL[10]	59.3*	4.8
FOLFOX4/XELOX/ bevacizumab	NO16966[7,19]	47	6.3
FOLFIRI/bevacizumab	First BEAT[20]	NA	5.1
FOLFOXIRI/bevacizumab	GONO[21]	76	14

**For wild-type KRAS. FOLFIRI = folinic acid, 5-FU and irinotecan; FOLFOX4 = oxaliplatin, leucovorin, and fluorouracil; FOLFOXIRI = irinotecan, oxaliplatin and infusional 5FU/folinic acid; GONO = Gruppo Oncologico Nord Ovest; RR = response rate; XELOX = capecitabine plus oxaliplatin.*

In the randomized phase II multicenter OPUS trial,[11] the addition of cetuximab to FOLFOX4 was associated with a 2.5-fold increased chance for response compared with FOLFOX4 alone in patients with wild-type tumors (RR 61 versus 37%; p=0.011). Patients with mutant *KRAS* tumors did not benefit and may actually have been harmed by the addition of cetuximab (RR 33% versus 49% in the FOLFOX4-alone group; p=0.106).

The phase III COIN trial[12] is another study that has evaluated the effect of the addition of cetuximab to oxaliplatin-based regimens in first-line treatment of advanced colorectal cancer. In contrast to the CRYSTAL and OPUS studies, this trial prospectively analyzed the data for *KRAS* status. The choice of fluoropyrimidine (either 5-FU or capecitabine) was decided by the treating physician prior to randomization (66% of the patients received oxaliplatin plus capecitabine). In patients with wild-type *KRAS* tumors, the addition of cetuximab to oxaliplatin-based chemotherapy was associated with a small increase in best overall response (64 versus 57%, p=0.049). The addition of cetuximab, however, was not associated with any significant improvement in OS or PFS.

Toxicities and Special Risks Associated with Bevacizumab and Cetuximab

Bevacizumab is associated with the potential for serious adverse events, which include an increased risk of bleeding and thrombotic events as well as hypertension, proteinuria, and gastrointestinal perforation. The fact that VEGF is involved in wound healing and liver regeneration has raised the theoretical concern that the use of pre-operative bevacizumab might increase post-operative morbidity after resection of hepatic metastases. Bevacizumab has a long half-life (20 days), and this must also be considered in the timing of the surgery.[13] Scappaticci and colleagues reviewed cases in which bevacizumab was administrated in combination with 5-FU/leucovorin-based chemotherapy 28–60 days after primary surgery. They concluded that such use was not associated with an increased risk for wound complications. If major surgery was carried out during treatment, however, 13% of patients experienced problems with healing.[14] Three small retrospectives studies showed no higher post-operative complication rates after liver resection with pre-operative use of bevacizumab, but the median time between

bevacizumab administration and surgery was more than six weeks in all studies.[15–17] A phase II trial evaluating pre-operative bevacizumab with capecitabine and oxaliplatin showed that treatment could be safely given until five weeks before hepatectomy.[18]

Most experts agree that even major surgery may be performed safely if bevacizumab is stopped six to eight weeks (more than two half-lives) before surgery. In practice, chemotherapy plus bevacizumab is often initially administered to patients with hepatic mCRC, while the bevacizumab is withheld during the last three or so cycles before surgery.

Cetuximab use is also associated with potentially severe toxicities, including skin reactions, diarrhea, infusion reactions, and (more rarely) lung toxicity. Inhibition of EGFR does not inhibit wound healing and is not a special concern in considering pre-operative use of this agent.

Metastasectomy Data

Bevacizumab

In the NO16966 trial discussed previously, 6.3% of patients with initially unresectable metastases underwent R0 surgery after treatment with bevacizumab plus oxaliplatin-based chemotherapy versus 4.9% of those treated with a fluoropyrimidine plus oxaliplatin alone.[7,19] In the First BEAT study, 6% of all evaluable patients underwent R0 resection, as did 8.0% of patients who received oxaliplatin-based chemotherapy plus bevacizumab and 5.1% of patients who received irinotecan-based chemotherapy with bevacizumab.[20] In a phase II trial, the Gruppo Oncologico Nord Ovest (GONO) reported a 76% RR with a 14% secondary R0 metastasectomy rate with the addition of bevacizumab to FOLFOXIRI (irinotecan, oxaliplatin and infusional 5FU/folinic acid).[21] However, a pooled analysis of two phase II and one phase III trials has shown that the FOLFOXIRI-alone regimen was associated with a high RR (70%) and 19% secondary metastasectomy rate.[22]

Cetuximab

In the CRYSTAL study, the rate of eventual metastasectomy was higher in patients receiving cetuximab versus chemotherapy (7.0 versus 3.7%), as was the rate of R0 resection with curative intent before disease progression (4.8 versus 1.7%; p=0.002). This analysis was performed for all patients, however, regardless of *KRAS* status.[10]

In the OPUS trial, patients with *KRAS* wild-type tumors had an increase in R0 resection rates (9.8 versus 4.1%) when given cetuximab plus FOLFOX4 compared with FOLFOX4 alone.[11] By contrast, in patients with *KRAS* mutant tumors, R0 resection rates were similar in both treatment arms (1.9 versus 2.1%).[11] In the CELIM randomized phase II study,[23] patients (71% wild-type *KRAS*) with non-resectable liver metastases were randomized to receive FOLFOX6 with cetuximab or FOLFIRI with cetuximab as first-line therapy. The confirmed RR was 62% for all patients and 70% for wild-type *KRAS* patients. Thirty-four percent of all patients underwent an R0 liver resection (see *Table 1*).

Conclusions

The use of a biologically targeted agent in addition to standard chemotherapy in mCRC patients being considered for liver metastases resection is a reasonable option and will probably become the standard of care. For now, however, it is not clear whether bevacizumab or cetuximab should be preferentially selected.

While RR is not a perfect surrogate for OS in mCRC, it may be an important factor among patients with potentially resectable disease. Folprecht and associates showed that objective response was a strong predictor of resectability in mCRC patients undergoing pre-operative conversion chemotherapy.[24]

Certain situations lend themselves to the use of one drug or the other. Patients whose tumors harbor *KRAS* mutations should be offered bevacizumab because they do not benefit from cetuximab and may actually be harmed by this agent. Patients with wild-type *KRAS* who are being considered for conversion therapy should be offered cetuximab. Even though this agent has not been directly compared with bevacizumab, it seems to have superior single-agent and combination response data. Patients with resectable, wild-type *KRAS* CRC being offered true neoadjuvant systemic therapy may at this time be considered for either.

The current North American CALGB/SWOG co-operative group trial of best chemotherapy plus either bevacizumab or cetuximab in untreated metastatic disease patients has, as a secondary objective, the assessment of conversion to resectability rates. The results of this study will help guide treatment decision-making in a small subset of mCRC patients.

Importantly, treatment must be individualized as always, taking into account the goals of pre-operative therapy, *KRAS* mutation status, and the toxicity profiles of each agent. ■

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