

Activity of Oxaliplatin Plus Capecitabine (CapeOx) With Lapatinib for Metastatic Colorectal Cancer: Results From Two Patients Treated on a Clinical Study

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Introduction

Colorectal cancer is the third most commonly diagnosed malignancy and the third leading cause of cancer death in the United States. Ninety-four percent of cases are adenocarcinomas, and more than half of patients have locoregionally advanced or metastatic disease at the time of diagnosis.² Of those who undergo surgery for localized disease, 30–50% recur either locally or with metastatic disease in the liver (20–70%) and/or lung (10–20%).^{3–5}

Recent advances in chemotherapy for metastatic colorectal cancer (mCRC) have included the introduction of oxaliplatin and irinotecan-based regimens as first-line treatment. Median overall survival (OS) rates have improved from approximately 10 months with fluorouracil (5-FU) alone to 20 months or more with newer regimens.^{6–13} Additional improvement in progression-free survival (PFS) and objective response rate (ORR) has been seen with the addition of cetuximab to the 5-FU, leucovorin, and irinotecan (FOLFIRI) regimen in first-line treatment.¹⁴ The use of cetuximab-containing regimens for mCRC may be further refined by testing tumors for KRAS mutations, as cetuximab appears to work exclusively against tumors with wild-type KRAS.¹⁵ Other advances include the addition of the anti-VEGF agent bevacizumab (Avastin, Genentech) to existing chemotherapy regimens. Adding bevacizumab to the 5-FU, leucovorin, and irinotecan (IFL) regimen resulted in a significant improvement in median OS in one large study.¹⁶ In another study, the addition of bevacizumab to 5-FU, leucovorin, and oxaliplatin (FOLFOX) improved PFS in the treatment of mCRC, though no benefit was seen in OS.¹⁷

Despite improvements in the treatment of mCRC, prognosis remains poor once the disease progresses after

first-line treatment. The response rate with second-line FOLFOX is only 15%, and second-line FOLFIRI has a response rate of just 4%; median PFS with either regimen in the second-line setting is less than 5 months.¹⁸ In another recent study, the combination of cetuximab and irinotecan, given after progression with first-line FOLFOX, showed an ORR of 16% and median PFS of 4 months.¹⁹ The addition of bevacizumab to FOLFOX has been shown to improve OS by approximately 2 months following the failure of irinotecan-based chemotherapy.²⁰ Although considerable progress has been made in the treatment of mCRC, other regimens and agents are clearly needed to further improve outcomes.

Lapatinib (Tykerb, GlaxoSmithKline) is a small-molecule inhibitor of both the epidermal growth factor receptor (ErbB1, EGFR) and ErbB2 (HER2/neu) tyrosine kinases. These receptors share a common pathway leading to cell proliferation. Studies have shown that EGFR and HER2/neu overexpression is associated with worse prognosis in many malignancies, including lung, head and neck, colon, breast, and prostate.^{21–23} It has also been shown that HER2/neu signaling is increased in colon cancer cell lines after EGFR blockade.²⁴ Cetuximab (Erbix, Bristol-Myers Squibb, Eli Lilly), which blocks the EGFR signaling pathway, has shown clear efficacy in the treatment of mCRC.²⁵ However, disrupting HER2/neu activity may offer additional benefit in treating mCRC by targeting tumors that overexpress HER2/neu with or without EGFR blockade, as well as tumors with mutated KRAS. In vivo studies also suggest that lapatinib sensitizes colon cancer cells to EGFR inhibitors and/or fluoropyrimidines like capecitabine.^{26,27} Thus, combining lapatinib with standard chemotherapy is a reasonable strategy.

Here we present 2 cases of mCRC patients with hepatic disease who demonstrated a significant clinical response to the regimen of capecitabine and oxaliplatin (CapeOx) plus lapatinib. These patients were treated at our institution under a phase I/II clinical trial protocol.

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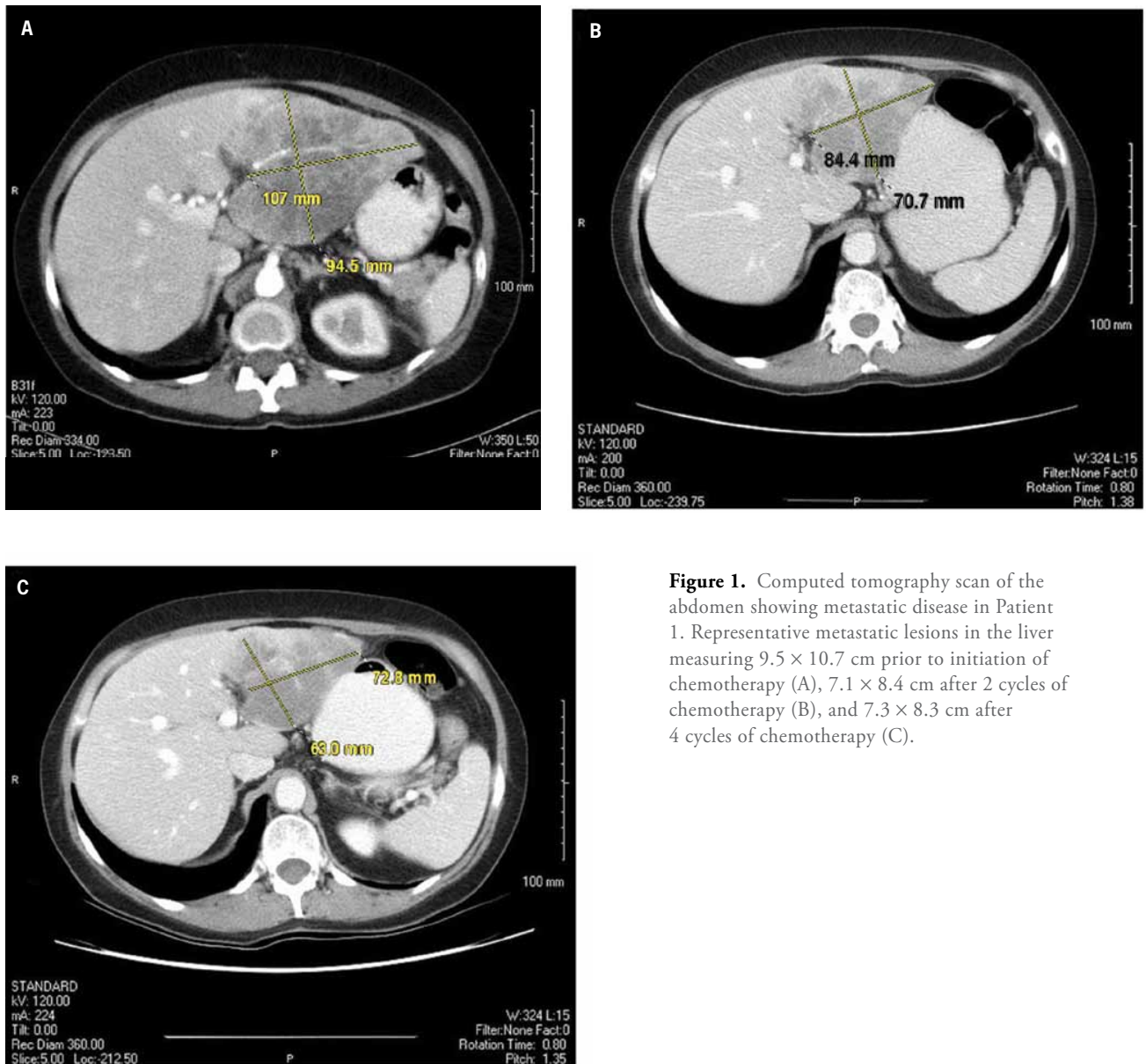


Figure 1. Computed tomography scan of the abdomen showing metastatic disease in Patient 1. Representative metastatic lesions in the liver measuring 9.5×10.7 cm prior to initiation of chemotherapy (A), 7.1×8.4 cm after 2 cycles of chemotherapy (B), and 7.3×8.3 cm after 4 cycles of chemotherapy (C).

Case Reports

Patient 1

A 59-year-old woman was diagnosed with mCRC with liver metastases in June 2008. Computed tomography (CT) imaging revealed diffuse infiltration of the left hepatic lobe and multiple discrete lesions on the right lobe. The diagnosis was confirmed by liver biopsy. She also underwent a colonoscopy, which found a large, near-obstructing mass of 15–20 cm from the anal verge.

The patient subsequently enrolled in the phase I/II study. Her treatment was started in late July, and

was given over a 21-day cycle as follows: capecitabine $2,000 \text{ mg/m}^2$ orally twice daily, days 1–14; oxaliplatin 130 mg/m^2 intravenously, day 1 only; and lapatinib $1,250 \text{ mg/day}$ (continuous). The first cycle of treatment was complicated by grade 2 nausea/vomiting and diarrhea, as well as grade 1 peripheral neuropathy. Due to these side effects, cycle #2 was given with a 25% dose reduction per study protocol, but was still complicated by grade 3 nausea/vomiting and diarrhea. CT imaging following cycle #2 showed a reduction in the size of the largest liver mass from 9.5×10.7 cm (Figure 1A) to 7.1×8.4 cm (Figure 1B).

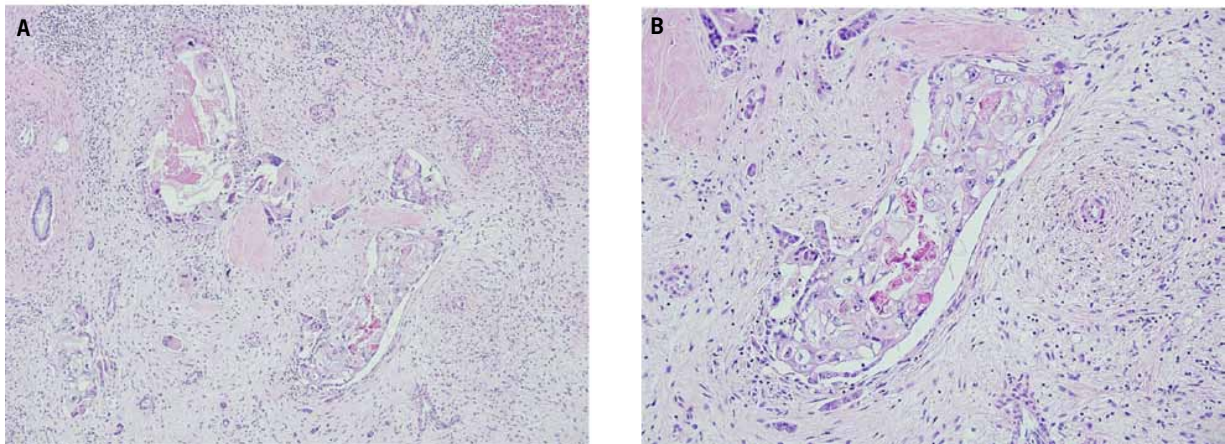


Figure 2. Hematoxylin and eosin stain of representative area of metastatic disease in liver at 10× (A) and 20× (B) after partial hepatectomy.

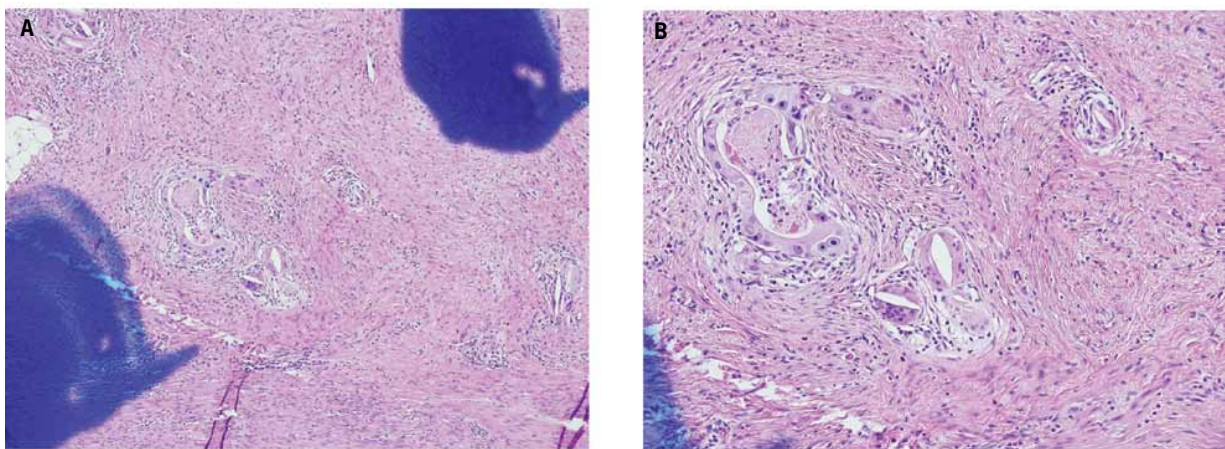


Figure 3. Hematoxylin and eosin stain of representative area of primary disease in colon at 10× (A) and 20× (B) after resection.

The patient received another 25% dose reduction for cycle #3. She tolerated treatment well in this cycle. Repeat CT imaging prior to cycle #4 showed continued improvement (Figure 1C). The patient's response to treatment was considered adequate enough to proceed with extended partial hepatectomy. She underwent exploratory laparotomy with left hemi-hepatectomy, wedge resection of section VI/VII hepatic metastases, cryoablation of section VII/VIII, and omental node biopsy. Pathology showed less than 1% residual carcinoma in the 8-cm hepatic mass (Figure 2). The colon specimen revealed 2-minute foci of carcinoma less than 1 mm each (Figure 3). The remaining liver tissue, omental biopsy, gall bladder, and all sampled lymph nodes were free of tumor. The patient underwent 2 additional months of chemotherapy postoperatively, and continues to have no evidence of disease by CT imaging at 29 months after surgery.

Patient 2

A 71-year-old woman was diagnosed with mCRC in March 2008 after she presented with rectal bleeding and underwent colonoscopy, demonstrating a circumferential colon mass. She underwent hemicolectomy for acute treatment, and was found to have evidence of liver metastases during surgery. Pathology confirmed the presence of metastatic disease to the liver, as well as 4/10 pericolic lymph nodes. CT imaging showed multiple masses in both lobes of the liver (Figure 4A).

The patient agreed to treatment on study and received cycle #1 of chemotherapy in June (same initial regimen/dosing as for Patient 1). The first cycle was complicated by grade 3 nausea and diarrhea, requiring a one-day admission for fluid replacement and symptom management. She started cycle #2 with a 25% dose reduction per protocol for associated toxicities. She tolerated this cycle well

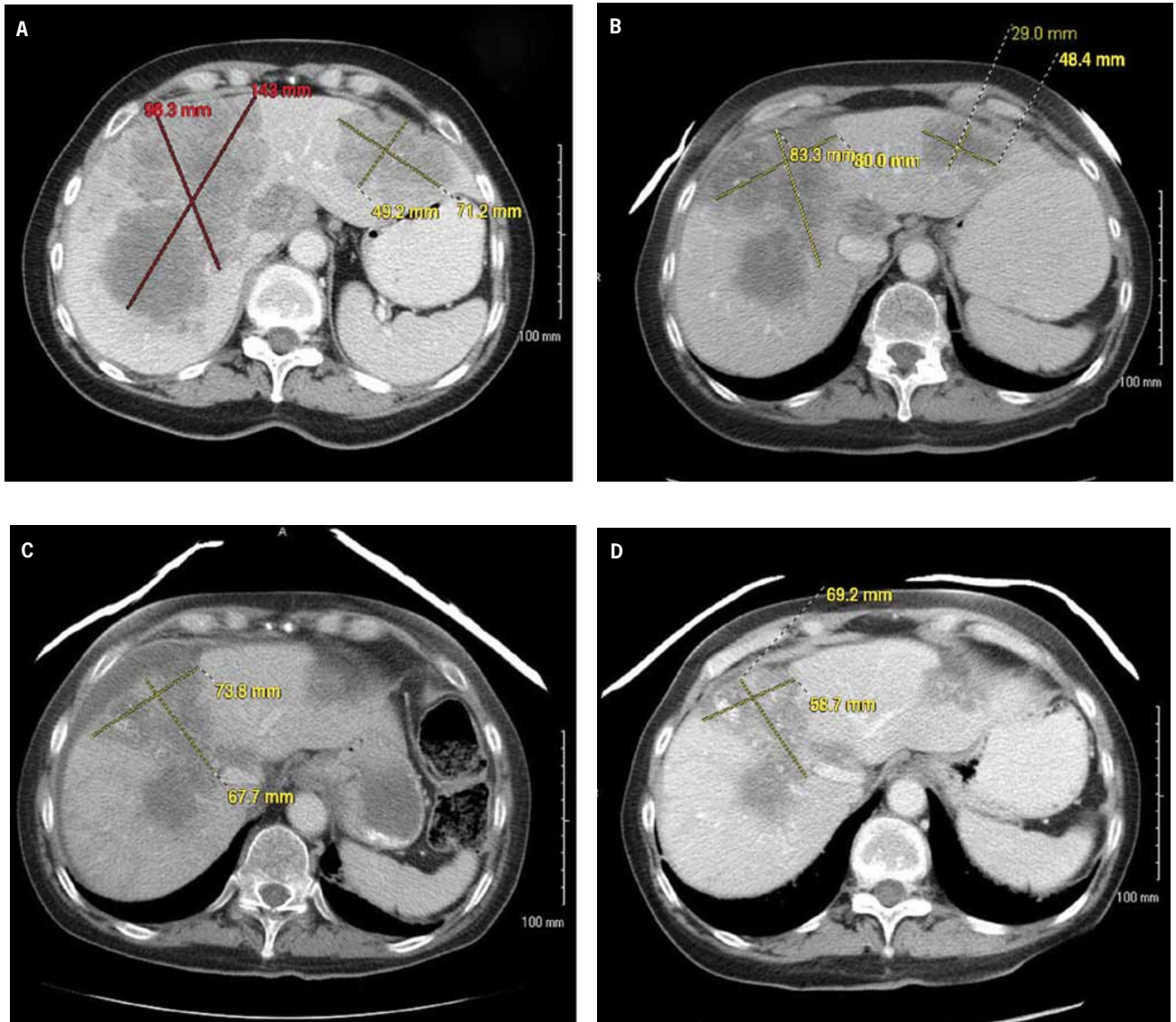


Figure 4. Computed tomography scan of the abdomen showing metastatic disease in Patient 2. Representative foci of metastatic disease in the liver measuring 14×9.6 cm prior to chemotherapy (A), 8.3×8.0 cm after cycle #2 of chemotherapy (B), 7.4×6.8 cm after cycle #4 of chemotherapy (C), and 6.9×5.9 cm 1 month after completion of therapy (D).

and was therefore treated with cycle #3 with no change in dosing. A CT scan performed prior to cycle #3 revealed significant improvement in disease, with a decrease in size of multiple metastatic nodules and lymph nodes. A representative intrahepatic mass in the left lobe that previously measured 7.1×4.9 cm (Figure 4A) had decreased to 4.8×2.9 cm (Figure 4B).

The patient's third cycle of treatment was uneventful, but she again developed severe diarrhea during cycle #4, leading to the decision to temporarily hold further chemotherapy. However, repeat CT scans in early September and the end of October showed continuing improvement,

even after the patient was off chemotherapy. Specifically, the largest lesion in the anterior right hepatic lobe decreased from 14×9.6 cm (Figure 4A) to 7.4×6.8 cm (Figure 4C) and subsequently to 6.9×5.9 cm (Figure 4D). A lesion in the medial left hepatic lobe shrank from 4.7×3.0 cm (Figure 5A) to 3.8×2.6 cm (Figure 5B). An additional lesion in the inferior right hepatic lobe that had previously measured 3.0×2.5 cm (Figure 6A) decreased to 2.4×2.1 cm (Figure 6B). Based on her continued improvement, the patient was given an extended break from chemotherapy.

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(Mohammed et al, continued from page 495)

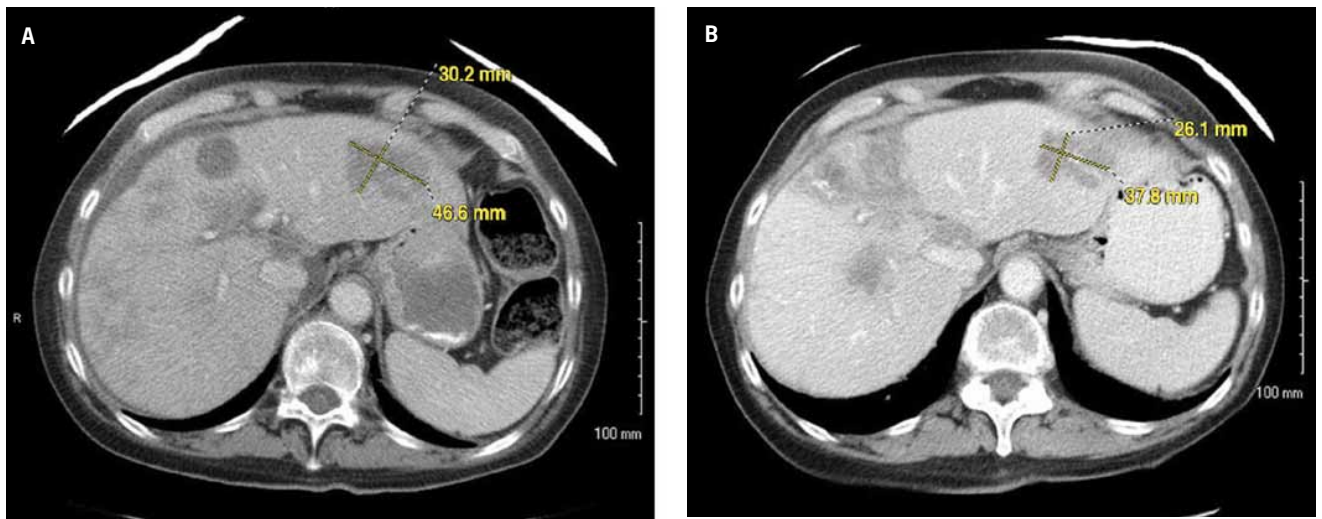


Figure 5. Computed tomography scan of the abdomen showing metastatic disease in Patient 2. Representative focus of metastatic disease in the liver measuring 4.7×3.0 cm after cycle #4 (A) and 3.8×2.6 cm 1 month after completing therapy (B).

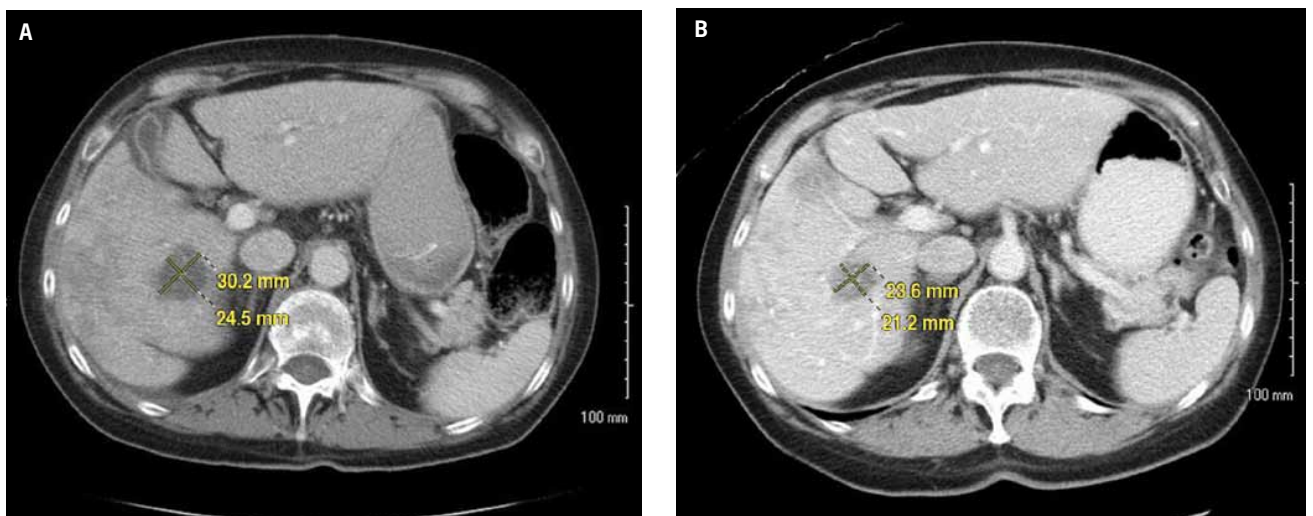


Figure 6. Computed tomography scan of the abdomen showing metastatic disease in Patient 2. Representative focus of metastatic disease in the liver measuring 3.0×2.5 cm after cycle #4 (A) and 2.4×2.1 cm 1 month after completing therapy (B).

Discussion

Significant progress has been made in the treatment of mCRC; however, alternative regimens need to be developed, as outcomes after disease progression remain poor. Studies have shown comparable efficacy and tolerability of capecitabine compared to 5-FU with leucovorin,^{12,13} and oxaliplatin is an established component of combination regimens for treatment of mCRC. Lapatinib, a dual inhibitor of EGFR and HER2/neu, has shown poten-

tial benefit in many different malignancies, including colorectal cancer.

The patients described here were treated as part of a phase I/II trial at our institution. Both patients showed significant improvement in disease status within a few months of beginning the CapeOx/lapatinib regimen. However, both experienced significant gastrointestinal toxicities, including nausea, vomiting, and diarrhea at the original dose. They were able to better tolerate the regimen with dose reductions of 25–50%. In both cases,

tumor reduction of more than 30% was noted. One patient currently has no evidence of disease following partial hepatectomy, after originally presenting with profound tumor burden in the liver, and the other patient also had an impressive partial response, including ongoing regression of metastatic lesions, for 4 months after treatment was held.

This particular trial has been suspended to further accrual at present, pending revisions to dosing guidelines in the study protocol. The protocol will then require Institutional Review Board re-evaluation. While the study protocol may require modification to further minimize toxicity, initial results with the addition of lapatinib to CapeOx are promising. The contribution of lapatinib to this regimen's efficacy is uncertain at present, but hopefully will become clearer with further investigation.

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Review Lapatinib in Metastatic Colorectal Cancer—Another Strategy for Disease Control?

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Introduction

Mohammed and colleagues present 2 interesting cases of metastatic colorectal cancer treated with capecitabine, oxaliplatin, and the dual epidermal growth factor recep-

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tor (EGFR) and HER2/neu receptor inhibitor lapatinib (Tykerb, GlaxoSmithKline).¹ The patients were treated as part of a phase I/II study. In the first case, a partial response was achieved prior to definitive liver surgery, which was followed by further chemotherapy for 2 months. There was no evidence of disease on a later computed tomography (CT) scan. The second case demonstrated a remarkable partial response in the size of liver metastases, with continued improvement off treatment. The treatment combination is attractive, as both lapatinib and capecitabine can be administered orally, thereby minimizing clinic visits and the need for central venous access devices.

Rationale for Targeting the EGFR and HER2/neu Receptors in Metastatic Colorectal Cancer

Lapatinib is a small molecule inhibitor of the intracellular tyrosine kinase domains of EGFR and HER2 receptors, which inhibits downstream signaling through the RAS/RAF/MEK/MAPK and PI3K/AKT pathways. EGFR is overexpressed in 60–80% of colorectal cancers, where it promotes cell survival and disease progression. Monoclonal antibodies that target the extracellular domain of EGFR, such as cetuximab (Erbix, Bristol-Myers Squibb/Eli Lilly) and panitumumab (Vectibix, Amgen) are associated with therapeutic efficacy when given in combination with 5-fluorouracil (5-FU)-based chemotherapy. Mutations in KRAS have been proven to be a negative predictive factor for response to both these monoclonal antibodies.² HER2 overexpression is a key target in metastatic breast cancer, and has also shown promise in gastric cancer. The evidence for its role as a therapeutic target in metastatic colorectal cancer is less clear-cut. However, a recent study by Marx and colleagues showed that in 1,439 cases of colorectal cancer, HER2 amplification was detected in only 2.5% of cases and overexpression was detected in 2.7% of cases.³ Targeting HER2 and EGFR simultaneously is a valid approach, as HER2 is thought to be the preferred dimerization partner for other members of the HER family (including EGFR), leading to intensification of cell signaling, and prolonged inhibition of the EGFR receptor has been shown to promote cell growth via the HER2 pathway.⁴

The current treatments for metastatic colorectal cancer typically involve infusional 5-FU given in com-

bination with oxaliplatin or irinotecan with or without a biologic agent such as cetuximab or bevacizumab (Avastin, Genentech; which inhibits the action of vascular endothelial growth factor). Capecitabine is a pro-drug of 5-FU that is thought to be preferentially activated in tumor tissue due to the presence of the enzyme thymidine phosphorylase. A meta-analysis has shown similar efficacy in terms of progression-free survival and overall survival with capecitabine compared to infusional 5-FU, though response rates were significantly lower with capecitabine.⁵ Although there are distinct advantages in terms of its oral formulation, it does have significant dose-limiting toxicities, such as diarrhea, thrombocytopenia, and hand-foot syndrome; infusional 5-FU is associated with higher rates of neutropenia. The combination of capecitabine and oxaliplatin in metastatic colorectal cancer is associated with response rates of 27–48%.⁵ The addition of lapatinib to this regimen was associated with significant gastrointestinal toxicity, in the form of diarrhea, which is not surprising given the previous reported toxicities seen with the combination of EGFR inhibition and capecitabine; the exact mechanism for this toxicity remains unclear.

Conclusion

The combination of cytotoxic chemotherapy and small molecule tyrosine kinase inhibitors such as lapatinib in colorectal cancer may present a new strategy for treatment. Both patients presented here responded to the lapatinib/capecitabine/oxaliplatin combination; however, additional larger studies are required to determine if the efficacy is superior to standard therapy and to establish the optimum dosing schedule to minimize toxicity.

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