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First-line combination treatment of colorectal cancer with hepatic metastases: Choosing a targeted agent

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Colorectal neoplasms;
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Summary A 56-year-old man has a history of bright red blood per rectum for 3 months; computed tomography reveals 4 hepatic lesions in the right lobe, the largest measuring 5.5 cm. Chemotherapy may accomplish sufficient reduction of the hepatic tumor burden to enable surgery with curative intent. Both FOLFOX and FOLFIRI are appropriate, highly active first-line regimens that may also be administered as second-line salvage chemotherapy. Research continues to evaluate the safety and efficacy of combining bevacizumab and cetuximab or adding them singly to established chemotherapy regimens. In patients with initially unresectable tumors, a direct relationship of response to chemotherapy with attainment of resectability supports a strategy of using the most active regimens in potentially curable patients. Literature confirms the importance of exposing patients to the most efficacious agents during the course of disease treatment. Genetic testing for specific mutations such as KRAS may be helpful for supporting a treatment decision to use cetuximab.

Patient scenario – case presentation:

A 56-year-old man came to our center with a history of bright red blood per rectum for 3 months. Colonoscopy revealed a sigmoid lesion; biopsy was positive for a moderately differentiated adenocarcinoma with mucinous features. Serum carcinoembryonic antigen level (CEA) was 25 units. Computed tomography revealed 4 hepatic lesions, all in the right lobe; the biggest measured 5.5 cm. Subsequent advanced imaging was negative for additional, extrahepatic metastases. Liver and renal function test results were within normal limits. There was no history of hypertension or diabetes, and the patient was not taking any medications.

Introduction

Colorectal cancer is metastatic (mCRC) at the time of diagnosis in over 60% of cases. When this occurs at distant sites, 5-year survival is approximately 10%.[1] The liver is the most common and, frequently, the sole site of metastatic disease in patients with CRC.[2] In contrast to patients with clearly incurable mCRC for whom palliative chemotherapy is offered to forestall disease progression, this patient scenario is representative of another situation that is often encountered in clinical practice: an individual whose macroscopic metastases appear to be confined to a strictly hepatic location, for whom effective chemotherapy may accomplish sufficient reduction of the hepatic tumor burden to enable surgery with curative intent.

> Effective chemotherapy may accomplish sufficient reduction of the hepatic tumor burden to enable surgery with curative intent

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Surgery, the gold standard of treatment for patients with hepatic metastases in whom it is indicated, significantly prolongs survival.[2] Despite considerable heterogeneity in prognosis following surgical resection, multiple, large metastases and a CEA level higher than 200 ng/mL are characteristics classically associated with decreased patient survival.[3] Criteria for resectability, a subject of much discussion, evolve in concert with the development of highly active chemotherapy agents and advances in surgical technique,[2,4] with the result that the population of patients with hepatic metastases who may be appropriate candidates for operation continues to expand. Currently, there is expert surgical consensus that one absolute contraindication to resection is the inability to ensure that at least 30% of functioning liver parenchyma remains after complete metastasectomy.[5,6]

Treatment options: 5-FU/LV, oxaliplatin, irinotecan, and targeted agents

The immediate challenge is to determine an optimal first-line regimen. For decades, chemotherapy based on 5-fluorouracil/leucovorin (LV) in combination with irinotecan (FOLFIRI) or oxaliplatin (FOLFOX) has been a foundation of cytotoxic treatment for mCRC. In recent years, this approach has been augmented by the availability of bevacizumab and cetuximab, monoclonal antibodies directed to specific biologic targets. Published data demonstrate that improved median overall survival correlates directly with exposure to these major cytotoxic agents at some point during the course of care, independent of the sequence of exposure.[7] Both FOLFOX and FOLFIRI are appropriate, highly active first-line regimens, and each may be administered as second-line salvage chemotherapy following the other without compromising survival benefits.[8] In prospective, randomized clinical trials, FOLFOX and FOLFIRI produce comparable response rates, time to progression, and overall survival of 17 to 21 months.[8,9]

Phase II, phase III, and retrospective reviews also demonstrate that systemic treatment with FOLFOX and FOLFIRI consistently enables a subgroup of patients with hepatic (as well as hepatic plus extrahepatic) metastases to undergo secondary resection with the resultant benefit of prolonged disease-free survival.[8–15] More recently, a phase III study of 244 patients with mCRC was conducted by the Gruppo Oncologico Nord Ovest. Baseline unresectability was a key inclusion criterion.[16] Patients received all active cytotoxic agents as initial therapy. Patients treated with FOLFOXIRI demonstrated significantly increased response rates that were among the highest reported in any randomized study of mCRC (FOLFOXIRI 60%, versus FOLFIRI 34%; $p < 0.0001$). A significant increase in the rate of radical surgical resection was observed overall and in the rate of R0 resection (compete excision) of hepatic metastases with FOLFOXIRI versus FOLFIRI alone (36% versus 12%; $p = 0.013$).[16] Toxicities were manageable in patients receiving this regimen, who were a median of 62 years in the FOLFOXIRI arm and 64 years in the FOLFIRI arm. However, toxicities might be more a matter of concern were this regimen to be administered to elderly patients with baseline performance status and other characteristics substantially different from those of patients in this study.[16]

The role of cetuximab and bevacizumab

The availability of bevacizumab, a recombinant monoclonal antibody targeting the vascular endothelial growth factor (VEGF), and cetuximab, an antibody inhibiting the epidermal growth factor receptor (EGFR), has led to improved response rates and prolonged survival when these agents are used in combination with irinotecan-based therapy in phase III treatment of mCRC,[17,18] extending to 28 months in a recent investigation.[19] The combination of FOLFOX plus bevacizumab for mCRC was shown to be highly effective in phase II study, achieving an overall response rate of approximately 68%, and allowing 8 of 53 treated patients (15%), all of whom were previously considered inoperable, to undergo metastasectomy.[20] There is recent phase III literature further supporting the use of bevacizumab in combination with oxaliplatin in first-line treatment of mCRC, demonstrating that the combination achieves statistically significant improvement in progression-free survival (approximately 1.5 months).[21]

The addition of cetuximab to irinotecan- or oxaliplatin-based chemotherapy has also yielded promising efficacy data in clinical trials of first-line treatment of mCRC.[22–25] A recent phase III, multinational, randomized trial evaluating FOLFIRI with or without cetuximab in the first-line treatment of 1217 patients with mCRC (the CRYSTAL trial) demonstrated improved PFS, improved response rate, and increased rate of secondary resection for the combination of FOLFIRI plus cetuximab versus FOLFIRI alone.[22,25] The combination of FOLFIRI plus cetuximab achieved a PFS (the primary endpoint) of 8.9 months compared with 8 months for FOLFIRI alone, a statistically significant difference ($p = 0.048$). Response rates (a secondary endpoint) with FOLFIRI plus cetuximab were 46.9% versus 38.7% for FOLFIRI alone ($p = .0038$). Among patients receiving FOLFIRI plus cetuximab, 6% underwent secondary resection, versus 2.5% of patients receiving FOLFIRI alone. Resection was classified as R0 in nearly three times the number of patients receiving FOLFIRI plus cetuximab (4.3% versus 1.5%; $p = 0.0034$).[22,25]

Research continues to evaluate the safety and efficacy of targeted agents in the treatment of mCRC, combining bevacizumab and cetuximab or adding them singly to established chemotherapy regimens. The combination of FOLFOX plus cetuximab is currently undergoing phase III investigation in a major multicenter European study enrolling patients with stage III colorectal cancer (PETACC-8)[26]; the addition of cetuximab to capecitabine, oxaliplatin, and bevacizumab in the first-line treatment of advanced CRC is under investigation by the Dutch Colorectal Cancer Group (CAIRO2).[27] Preliminary results from CAIRO2 are notable for suggesting that the addition of both targeted antibodies to CapeOx leads to a decrease in PFS compared with CapeOx + bevacizumab alone.[28]

Adjunctive testing for molecular markers and patterns of gene expression holds immense promise for identifying patients most likely to benefit from chemotherapy plus