Intrahepatic Therapy for Resected Hepatic Metastases From Colorectal Carcinoma

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A significant number of patients with colorectal cancer will present with hepatic metastases as their only site of metastatic disease. Surgical resection in patients with a limited number of metastases will lead to long-term

Introduction

An estimated 130,200 people in the United States will develop colorectal cancer in the year 2000,[1] and approximately 15% to 17% of these will initially present with stage IV disease.[2] In addition, approximately 40% of patients undergoing potentially curative resection for stage II and III disease will subsequently recur.[3]

The liver represents one of the most common sites of disease recurrence in patients with colorectal carcinoma, and is a major cause of morbidity and mortality in this patient population. In an autopsy series of patients who died of colorectal carcinoma, 44% had liver metastases.[4] In 46% of those cases (20% overall), the liver was the only site of metastatic disease. Without treatment, patients with liver metastases have a median survival of 5 to 12 months.[5-7]

Surgical Resection

In a review of 1,001 patients undergoing resection of hepatic metastases at the Memorial Sloan-Kettering Cancer Center, Fong et al found that resection of a solitary metastasis was associated with the best prognosis.[8] The 5-year survival for this group of patients was 44%. Patients with more extensive disease had a shorter survival.

In a multi-institutional review, Hughes noted 5-year actuarial survivals of 37% for patients with solitary lesions, 34% for patients with two metastatic lesions (most of which were unilobar), 8% for those with three metastatic lesions, and 18% for those with four or more lesions.[9] Corresponding 5-year actuarial disease-free survivals were 36%, 32%, 0%, and 14%, respectively.

When patients with three metastatic lesions were grouped together with patients who had four or more metastatic lesions, the actuarial 5-year survival was 14%, and disease-free survival was 7%, respectively. This compares to the 35% actuarial and disease-free survival for patients with one or two metastatic lesions.

Regional Therapy

Patients who have undergone resection of colorectal metastases to the liver may be candidates for regional infusion therapy.[10-12] The pattern of recurrence after the first liver resection shows that 41% of subsequent recurrences involve only the liver.[13] Recent studies of patients undergoing hepatic artery infusion after resection report an improved survival as well as a decrease in hepatic recurrence compared with those receiving systemic therapy. These studies were built upon the prior observation of benefit from regional therapy in patients with unresectable liver metastases from colorectal carcinoma.[14]

The Mayo Clinic and North Central Cancer Treatment Group (NCCTG) conducted a trial of intrahepatic floxuridine (FUDR) vs systemic fluorouracil (5-FU) in patients with unresectable colorectal liver metastases.[14] This trial confirmed significantly higher tumor response rates for intrahepatic FUDR (55%) compared to systemic 5-FU (17%; \( P < .01 \), and significantly longer time to
hepatic progression with intrahepatic FUDR compared to systemic 5-FU. Despite the higher response rate with FUDR, no improvement in survival was seen due to the higher incidence of extrahepatic tumor progression in the FUDR-treated group.

Two additional phase III trials comparing intrahepatic vs systemic FUDR for the treatment of colorectal liver metastases yielded similar results.[15,16] However, systemic chemotherapy has improved with the advent of combination chemotherapy, and several controlled clinical trials have demonstrated a significant increase in objective tumor response rates when 5-FU is combined with leucovorin vs single-agent 5-FU.[17-19] and when used in the three-drug regimen of irinotecan (CPT-11, Camptosar)/5-FU/leucovorin.[20]

A pilot Mayo Clinic/NCCTG study of systemic 5-FU/leucovorin combined with hepatic artery infusion FUDR demonstrated that this regimen is tolerable.[21] Among 40 eligible patients who received therapy, 62% had regression of their liver metastases. Median time to tumor progression was 9 months, and median survival was 18 months. The toxicity was tolerable, and there were no cases of biliary sclerosis.

A prospective Mayo Clinic/NCCTG trial of systemic 5-FU and leucovorin combined with hepatic artery infusion FUDR following hepatic resection has now reached its targeted accrual of 96 patients (unpublished data).

Two randomized trials of hepatic artery infusion following surgical resection of hepatic metastases from colorectal carcinoma have been reported recently. In a study from Memorial Sloan-Kettering Cancer Center, 82 patients were randomized to systemic chemotherapy alone, with either bolus 5-FU and leucovorin or continuous-infusion 5-FU, vs 74 patients randomized to systemic chemotherapy combined with hepatic artery infusion FUDR.[22] A significant benefit was seen in patients receiving the combined therapy.

The median survival in the combined-therapy group was 72.2 months, compared with 59.3 months for those receiving systemic therapy alone. At 2 years, the rate of survival (free of hepatic recurrence) was 90% in the combined-therapy group compared with 60% in the systemic therapy-only group ($P < .001$). However, recurrence rates outside the liver appeared similar in both groups (Table 1).

In another study, patients with two to four resected hepatic metastases were randomized to resection alone vs hepatic artery infusion FUDR combined with systemic continuous-infusion 5-FU.[23] As in the Memorial Sloan-Kettering trial, this study showed a marked decrease in hepatic recurrence with hepatic artery infusion and a significant improvement in recurrence-free survival.

**Role for Oxaliplatin**

Recent experience with hepatic artery infusion combined with systemic chemotherapy suggests that, despite improved disease-free survival, both intrahepatic and extrahepatic recurrence of colorectal carcinoma continues to be a problem for patients undergoing resection of hepatic metastases. As such, better systemic regimens are needed.

Oxaliplatin (Eloxatin) is a platinum complex that has shown activity against a number of human and murine tumors in vitro and in vivo, including colorectal carcinoma-derived cell lines.[24,25] It possesses a higher cytotoxic potency on a molar basis than either cisplatin (Platinol) or carboplatin (Paraplatin), and is also active against various cell lines that have been selected on the basis of their resistance to cisplatin.[26,27]

**Clinical Trials**

In an ongoing randomized phase III trial, the combination of oxaliplatin, 5-FU, and leucovorin is being compared to 5-FU and leucovorin in a group of 420 previously untreated patients with advanced colorectal carcinoma. An interim analysis showed a significantly higher response rate in patients ($n = 210$) receiving oxaliplatin (50.7% vs 22.3%; $P < .001$).[28] However, the addition of oxaliplatin also
increased toxicity.[28]

Grade 3 neurosensory toxicity occurred in 18.2% of patients receiving oxaliplatin, grade 3/4 diarrhea in 11.9%, and grade 3/3 vomiting and mucositis in 5.8%. Grade 3/4 neutropenia occurred in 41.7% of patients receiving oxaliplatin and 5.3% of patients receiving 5-FU and leucovorin alone. These did not significantly impair quality-of-life parameters, and indeed, de Gramont and colleagues noted a reversal of grade 3 neurosensory toxicity in 74% (25/34) of patients.

Bismuth et al reported on the potential surgical resection of initially unresectable liver metastases from colorectal carcinoma in a group of patients receiving neoadjuvant chemotherapy with oxaliplatin, 5-FU, and leucovorin.[29] A total of 330 patients with advanced disease that was determined to be unresectable by surgical evaluation were enrolled in the trial. All patients were initially treated with chemotherapy, and responses were assessed every three courses; a surgical resection was considered after each assessment.

A total of 53 patients demonstrated sufficient response to chemotherapy to allow for surgical exploration. This included a group of 13 patients who were known to have associated extrahepatic disease. The surgical complication rate was 26%, with no operative mortality. The cumulative 3-year and 5-year survival rates were 54% and 40%, respectively, including patients with known extrahepatic disease. Despite the fact that this was a selected group of patients, these findings were quite provocative given the overall dismal prognosis for this group of patients.

Conclusions

The above studies showed (1) improved survival following resection of hepatic metastases from colorectal carcinoma, (2) improved survival with the combination of hepatic artery infusion FUDR and systemic chemotherapy, and (3) the significant activity of oxaliplatin, 5-FU, and leucovorin in metastatic colorectal carcinoma. Based on these findings, the NCCTG is conducting a study of hepatic artery infusion FUDR alternating with systemic oxaliplatin, 5-FU, and leucovorin in patients undergoing resection of hepatic metastases.

Other groups are performing additional studies exploring the role of hepatic artery infusion using oxaliplatin.[30] These studies offer hope of increased survival for patients with resected hepatic metastases from colorectal carcinoma ([Table 2].[22,31-33] The use of oxaliplatin-based systemic therapy also offers the potential for a greater reduction in the incidence of extrahepatic metastases following resection of hepatic metastases.

References:


23. Kemeny MM, Adak S, Lipsitz S, et al: Results of the intergroup [Eastern Cooperative Oncology Group (ECOG) and Southwestern Oncology Group (SWOG)] prospective randomized study of surgery


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