Defining the Role of Hepatic Arterial Infusion Chemotherapy in Metastatic Colorectal Cancer

In their article, Drs. Whisenant and Venook review data regarding the value of hepatic arterial infusion (HAI) chemotherapy for hepatic colorectal metastases. In fact, their analysis reveals the absence of any material progress in HAI therapy since the first reports of continuous infusion of chemotherapy through the hepatic artery.[1] During the same period, there has been dramatic improvement in hepatic imaging, outcome from hepatic resection, systemic chemotherapy, and survival following treatment of hepatic colorectal metastases. Failure of HAI therapy to advance in parallel with other treatments for liver metastases—whether used prior to or after resection, or as definitive treatment for unresectable disease apparently confined to the liver—suggests a limited role for HAI therapy in this disease. Several points warrant discussion.

In the treatment of unresectable disease, HAI therapy has failed to live up to its initial promise, and is now clearly losing ground to constantly improving systemic chemotherapy. Irinotecan (Camptosar) and oxaliplatin (Eloxatin), when used in combination therapy with fluoropyrimidines, can yield high response rates (54% to 56%) and a median survival of 22 months with acceptable toxicity.[2] Recently approved targeted therapies for colorectal cancer—including bevacizumab (Avastin), an anti-vascular endothelial growth factor monoclonal antibody, and cetuximab (Erbitux), a monoclonal
epithelial growth factor receptor antibody-have further increased the prospects for higher tumor response rates. The best reported response rates using HAI chemotherapy (from the centers with the greatest experience with this mode of therapy) are 50% to 62%[3,4] in studies that date from the late 1980s, and have not consistently been reproduced (even by the same authors). The most recent multicenter study of HAI chemotherapy reported a response rate of only 48% and a median survival of 22.7 months,[5] similar to leucovorin/fluorouracil (5-FU)/oxaliplatin (FOLFOX) or leucovorin/5-FU/irinotecan (FOLFIRI).[2] Furthermore, these response rates are achieved only in selected patients who will tolerate laparotomy (systemic chemotherapy is available to patients with less favorable performance status), and only at the expense of an added layer of complications related to pump placement and subsequent HAI chemotherapy. Complications and Toxicity The potential complications and toxicity of HAI chemotherapy cannot be overemphasized, and have not improved significantly over time. In the most recent update of the experience at Memorial Sloan-Kettering Cancer Center, the technical complication rate related to insertion of implantable pumps remains 12%,[6] no different from the 10% rate reported by Kemeny nearly 10 years earlier.[7] Complications of the HAI chemotherapy also remain unacceptably high. Gastritis (25%), ulcer (9%), diarrhea (5%), and the dreaded biliary sclerosis (11%) are consistent and persistent potentially serious complications of therapy[8] that may also prohibit the appropriate subsequent deployment of systemic therapy. In Kemeny's important study in the New England Journal of Medicine, wherein HAI chemotherapy was investigated as an adjuvant to hepatic resection, only 26% of patients received the therapy, 4 of 74 patients developed biliary strictures (5.5%), and two late deaths (2.7%) occurred as a result of hepatic failure. Pump infections, hepatic artery thrombosis, catheter displacement, and intraabdominal hemorrhage complicated treatment in 14 of 74 patients (19%).[9] Similarly, in the series from Duke University, 4 of 21 patients (19%) treated with HAI therapy required chronic indwelling stents for biliary strictures, and one patient died with liver failure (4.8%).[10] In comparison, it should be noted that the mortality for FOLFOX or FOLFIRI is ≤ 1.1%, while two large multicenter trials of irinotecan plus bolus 5-FU/leucovorin (Saltz regimen) reported treatment-related mortality of 3.1% and 2.5%, respectively. [11] Preoperative Use of HAI Chemotherapy Similarly, support for use of HAI chemotherapy before surgery is lacking. HAI chemotherapy is not efficient in downstaging unresectable disease to enable resection. In over 300 collected cases from the University of San Francisco reported by Drs. Whisenant and Venook in the accompanying article, <1% were explored for possible resection and presumably fewer resected as a result of response to HAI chemotherapy. The abovementioned toxicity to the liver and bile ducts may preclude patients from safe resection even when tumor response occurs.[12,13] In contrast, we have shown that perioperative complications are not significantly increased following hepatic resection in patients who have undergone preoperative systemic chemotherapy.[14] It is clear that as experience with HAI chemotherapy has evolved, this modality has not enabled subsequent downstaging and hepatic resection at a rate that compares to the initial report by Bismuth (16%)[15] or to the rate of resection following modern chemotherapy in Europe (51% of 151 patients treated with chronomodulated oxaliplatin-based chemotherapy were explored, 38% underwent complete resection)[16] or in the United States (33% underwent complete resection following FOLFOX).[17] Postresection Adjuvant Treatment With HAI The rationale for postresection adjuvant treatment with HAI therapy is flawed for three major reasons. First, with complete resection, hepatic-only recurrence has fallen from about 36% in collected series before 1986[18] to only 11% in our latest series.[19] Otherwise stated, the majority of patients fail with extrahepatic disease as a component of their recurrence, which reiterates the need for systemic rather than regional treatment after complete resection. Second, the premise that HAI chemotherapy treats tumors preferentially because of their dependence on arterial inflow to the liver applies only to large tumors, not to residual "micrometastatic" disease in the liver left after resection— it has been known since the 1950s that hepatic metastases < 3 millimeters in size derive blood from the portal vein, not the hepatic artery.[20] Third, pump complications, liver failure, and death negate the advances in safety and outcome from complete hepatic resection. Mortality of major hepatic resection is approaching zero[21] and outcome for hepatic resection is improving. Choti et al recently reported that 5-year survival for patients who underwent resection between 1993 and 1999 was 58%.[22] Similarly, the 5-year survival rate for patients at M. D. Anderson Cancer Center who underwent resection of colorectal liver metastases (1992-2002) was 58%.[19] As a result, the implantation of HAI pumps at M. D. Anderson has fallen dramatically over the past few years (see Figure 1). Conclusions In summary, in over 40 years, there has been minimal progress in the treatment of colorectal
metastases to the liver using HAI chemotherapy, for either unresectable disease, as neoadjuvant therapy before resection, or as adjuvant therapy following resection. There is no improvement in survival as compared to systemic treatment, and the risks for toxicity from HAI therapy—especially biliary sclerosis (5% to 19%) and death from liver failure (3% to 5%), even in centers with the largest experience—are not inconsequential. Furthermore, technical complications of pump placement occur in ≥ 10% of patients, and this rate has remained stable over time. In parallel, during this same interval there have been dramatic advances in outcome from surgery, with a near-zero mortality for extended hepatic resection. There have also been marked improvements in systemic and molecularly targeted chemotherapy which better address the systemic disease ultimately seen in the majority of those who initially present with colorectal metastases apparently confined to the liver.

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**References:**


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