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

Drs. Whisenant and Venook have provided us with a summary of the role of hepatic arterial infusion (HAI) chemotherapy for patients with metastatic colorectal cancer. In their abstract they state that there is confusion about whether HAI for unresectable liver metastases is useful, because European studies have been negative; they go on to say that the work in adjuvant therapy has mixed results. I would like to offer some different interpretations.

Primary Treatment for Unresectable Liver Metastases

In discussing primary treatment, one must analyze the original trials with HAI, ascertain why they did not show an increase in survival, and then look at the evidence from the new studies. In reviewing the old studies, the Whisenant article does not extensively discuss the flaws in the old studies. There were seven old randomized studies. The two largest American studies[1,2] allowed a crossover to HAI after progression on systemic therapy, which made it difficult to find survival differences. A number of the studies were very small (less than 70 patients), which makes evaluation of survival differences difficult. I do not agree with the statement from the Whisenant article claiming that hepatobiliary toxicity led to no increase in survival. For example, in the study conducted at Memorial Sloan-Kettering Cancer Center (MSKCC), patients who were unable to cross over to HAI after failure on systemic therapy had a significantly lower survival than the patients who crossed over: 8 vs 17 months, respectively (P = .014).[1] In reviewing the new randomized studies from Germany and England comparing HAI to systemic therapy, the authors mention that a third of the patients in the German study and 37% of patients in the English study did not receive hepatic arterial therapy in the HAI arm and yet are included in the survival data. Obviously this would impact greatly on the survival statistics in these studies. They also fail to point out that the English study[3] used fluorouracil (5-FU) and not floxuridine (FUDR), which has a much lower hepatic extraction rate and is an inferior drug for HAI therapy. The new Cancer and Leukemia Group B study compared HAI therapy with FUDR, leucovorin, and dexamethasone to systemic 5-FU/leucovorin. There was a significant increase in a median survival of 24.4 months for the HAI group and 20 months for the systemic group (P = .003). This was a group of patients with poor clinical prognostic characteristics: 78% of patients presented with synchronous liver metastases (ie, their liver metastases were discovered with their primary) and 70% had more than 30% of their liver involved with tumor. The systemic group in this study started with 5-FU/leucovorin alone, but 86% of the patients went on to receive irinotecan and 46% oxaliplatin. Therefore, most of the patients had access to two or all three active drugs. Even so, the HAI group had a higher median survival. Twoyear survival was 56% for HAI and 38% for systemic therapy[4].

HAI in Second-Line Therapy

The role of HAI in second-line therapy was not discussed in the paper by Drs. Whisenant and Venook. Currently, our newer agents such as irinotecan (Camptosar), oxaliplatin (Eloxatin), or cetuximab (Erbitux), when used as second-line therapy, produce response rates ranging from 9% to 22%[5-7] with 1-year survivals not higher than 43% in the second-line setting. When HAI is used concurrently with systemic irinotecan or oxaliplatin in the second-line setting, response rates of 74% to 86%[8,9] have been reported; 1-year survivals of 86% and 84% can be seen, even in the second-line setting. If studies are to be done in the future comparing HAI to systemic chemotherapy with the new drugs, one should also consider combining HAI plus systemic therapy. Preoperative HAI

These authors discuss HAI in the preoperative setting. They reference a paper that was a retrospective paper spanning 15 years, which is really not a good indication of whether this treatment can be used in this setting. This year, we will present what happened to a group of 44
patients receiving second-line therapy with HAI and systemic oxaliplatin combination chemotherapy. Nine patients who were initially unresectable were able to undergo liver resection without complications. [10] HAI as Adjuvant Therapy After Liver Resection

Drs. Whisenant and Venook discuss in detail the German trial that compared HAI therapy with a port (not a pump) and used 5-FU (not FUDR). The German trial[11] was negative. However, if one looks at the actual number of patients that were treated in the HAI arm, only 74% actually started treatment and only 30% completed treatment. All of these patients, however, are included in the survival data. When looking at patients who actually received treatment vs the control group, there was a difference in time to progression for the HAI treated group. In the MSKCC study, 156 patients were actually randomized and all these patients are in the study.[12] The end point of this trial was 2 year-survival. The 2-year survival in the HAI plus systemic group (HAI + SYS) was 86% vs 72% in the systemic alone group (SYS) (P = .02). The median survival was 68.4 months in the HAI + SYS group and 58.8 months in the SYS group. Five- and ten- year survivals are currently 56% and 40% for the HAI + SYS group and 45% and 20% for the SYS group. The 5-year updated hepatic disease-free survival is 70% for the HAI group and 40% for the SYS group (P = .0001). In the Intergroup study,[13] 109 patients were randomized to systemic 5-FU and HAI FUDR and dexamethasone; 34 patients were excluded intraoperatively because of extrahepatic disease or other reasons. When analyzing the whole group, there was no difference in median survivals. However, in patients who actually entered the trial (after excluding the 34), there was a 4-year disease-free recurrence of 46% for the treated group vs 25% for the control group (P = .04). This trial and the MSKCC trial both demonstrate an increase in disease-free survival. The median disease-free survival presently in the MSKCC trial is 34.7 months for the HAI group and 17.2 months for the systemic group (P = .01). Conclusion

In conclusion, there is only one large study for first-line therapy that compares the use of HAI FUDR with a pump to systemic therapy without a crossover. The median survival for HAI therapy in that study was 24.4 months,[4] which is higher than that obtained with the other national studies using some of the new drugs. For second-line therapy, there are presently no other treatment modalities that produce the response rates and survivals that can be achieved with HAI and concurrent systemic chemotherapy.[7,8] For adjuvant therapy after liver resection, there are two large American studies using a pump and HAI FUDR that do demonstrate a significant increase in hepatic disease-free survival and overall disease-free survival. Some drugs are now being approved by the US Food and Drug Administration just on the basis of improvement in disease-free survival. Neither study was large enough to answer the question of 5-year survival, but one demonstrated a significant 2-year survival.[12]

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