ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Colorectal Cancer In Focus

Melphalan for Colorectal Metastases to the Liver

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H&O What is the optimal route of administration of melphalan?

JP The reality with melphalan administration is that although it is a great drug, because it is a nonspecific alkylating agent, it is difficult to deliver it systemically in doses that are effective for a variety of gastrointestinal cancers, most specifically colorectal cancers. Because of this, systemic administration of melphalan has no value and is very toxic to the bone marrow. When melphalan is given intra-arterially—a process referred to as *isolated hepatic perfusion* (IHP)—it is possible to deliver very effective dosing ranges of the drug into the liver. Through a variety of clinical trials, we have been able to show that even as second- or third-line therapy, the response rates are near 65%.

In IHP, the liver is surgically isolated by a laparotomy with clamps that control the inflow and outflow of blood. In other words, the liver is put on a "heart-lung bypass." From phase I and II trials, we know that there is virtually no systemic exposure of melphalan with this procedure; only the liver (not bone marrow or gastrointestinal mucosa) receives bone marrow–ablative doses of melphalan. Sometimes, after IHP, an intrahepatic pump or port is implanted, which in addition to perfusion, administers local chemotherapy through a process of hepatic arterial infusion.

Percutaneous hepatic perfusion (PHP) is also a method of direct drug delivery to the liver, but it is not done through a surgical procedure. The minimally invasive procedure involves infusion into the hepatic artery so that the portal vein flow and the hepatic artery flow are intact. The blood that leaves the liver to the hepatic veins is controlled by a catheter that is placed in the retrohepatic vena cava. The blood is subsequently filtered of melphalan and re-administered to the patient through a jugular catheter. The difference between PHP and IHP is that after IHP is performed, the remaining blood in the circuit gets flushed out and never returns to the patient's systemic circulation. With the percutaneous approach, the blood gets filtered and is returned to the patient. It is known that 80% of the drug gets filtered with PHP, but 20% ends up in the systemic circulation and leads to some, albeit manageable, toxicity.

PHP is a procedure that can be performed multiple times. In our phase I and II studies, we set the paradigm where 4 procedures would be performed: 2 treatments approximately 4–5 weeks apart, followed by evaluation of response, and a subsequent third and fourth treatment for those patients with stable disease or any degree of response. These treatments were given as a salvage therapy for patients who were refractory to systemic chemotherapy (at least one irinotecan and oxaliplatin-containing regimen).

H&O What kinds of results were seen from these studies of PHP and IHP?

JP The response rates for colorectal cancer were not good in these trials, as the data are very immature. Not enough patients were enrolled in our studies because the majority of CRC patients were treated in an era of open liver perfusions, and thus there were only a handful of patients being treated on the PHP protocol. The study population consists of 12 patients with a response rate of approximately 40%. Because the patient population was very chemorefractory, multiple patients discontinued the study due to end-stage status.

The advantage of performing an IHP is that the inflow for this procedure is through the gastroduodenal artery. Hence, after IHP, we were able to implant the hepatic artery infusion pump, which we felt would provide therapeutic benefit when added to perfusion, based on the available data. In patients with osteomelanoma and neuroendocrine tumors, there were a great deal of data for the percutaneous approach, but because of the protocol and data that suggested that perfusion plus a hepatic arterial infusion through a pump was superior to perfusion alone, we have been less aggressive about moving the percutaneous approach to frontline therapy above open liver perfusion.

H&O Is there evidence of efficacy in melphalan in combination with systemic chemotherapy?

JP A large number of patients with CRC, in whom we performed IHP, had the procedure with a placement of a hepatic artery infusion pump. The patients received a perfusion, recovered, were assessed for toxicity and response, and subsequently, went on to a protocol of 14 days of hepatic artery infusion therapy and a monthly dose of fluorouracil (5-FU), leucovorin, oxaliplatin (FOLFOX) or 5-FU, leucovorin, and irinotecan (FOLFIRI) for 6 months. Thus, the majority of the robust data we have are with the combination of perfusion, systemic chemotherapy, and local chemotherapy by hepatic arterial infusion (pump).

H&O What kind of research is your group currently involved with?

JP Currently, at the University of Pittsburgh Medical Center, we have a phase II protocol sponsored by the National Cancer Institute that is looking at liver perfusions with oxaliplatin and 5-FU in patients with minimal oxaliplatin exposure. The patients included in the trial have liver-only disease, and are treated with perfusion with oxaliplatin and 5-FU, followed by systemic chemotherapy alternating with hepatic arterial infusion of floxuridine. We perform melphalan perfusions in cases where patients have had too much oxaliplatin, because oxaliplatin can be damaging to the liver. In general, the patients had to have had first-line systemic chemotherapy. Generally, the response rates for second-line systemic chemotherapy are very poor (10–15%); however, responses for IHP and the pump are approximately 65% (data from approximately 200 patients). Therefore, if patients did not respond to first-line systemic chemotherapy and still have viable disease or are growing through their treatment at the completion of first-line therapy, then they are candidates for perfusion and pump placement even before commencement of a second-line therapy.

H&O How does one decide on the appropriate timing for perfusion, and what are some prognostic factors that may aid in making this decision?

JP The studies that are available do not give us enough data to know for sure which prognostic markers to use for predicting response. We employ things like staging criteria and disease-free interval, along with colon versus rectal primaries, and node status of the primary tumor. However, we have not treated enough patients to determine which markers offer useful prognostic information. The majority of the patients in our studies who do not respond to therapy do have a minor response, and we have very few patients whose disease progresses during therapy. Although we have limited information on prognostic factors, it is important to screen for the presence of extrahepatic disease, as these patients are then excluded from liver perfusion.

H&O What do you see in the future for metastatic, chemorefractory patients and how can we improve their prognosis?

JP The direction we are taking in our studies of liver perfusions is toward getting higher doses of drug directly into the liver and in turn reducing systemic side effects. In patients who have a high volume of liver disease, liver perfusion allows us to examine 5-FU and oxaliplatin in combination with targeted therapies, to access tissue, and to study the tumor and drug delivery to the tumor in a very real time way. We are very excited to utilize these very effective agents and to deliver them to patients in a more dose-intense manner. The early findings from the oxaliplatin studies are

encouraging, and we plan to explore this agent further. Also, I think it will be important to study other agents that may allow us to sensitize patients to higher doses of chemotherapy when the main risk is the liver. There are numerous drugs available that increase the exposure to and absorption of melphalan, and combining them with other biologics in the metastatic patient is our goal.

Suggested Readings

Grover A, Alexander HR Jr. The past decade of experience with isolated hepatic perfusion. *Oncologist*. 2004;9:653-664.

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