

The re-birth of hepatic arterial infusion for colorectal liver metastases

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In the last 20 years there have been many advances in the treatment of colorectal cancer. Response rates of 12% with 5-fluorouracil (5-FU) and leucovorin (LV) have increased to at least 50% with a combinations of 5-FU/LV with Oxaliplatin or Irinotecan (CPT), +/- Bevacizumab, Panitumumab or Cetuximab. However, the median survival, though an improvement from 14 months up to 26 months, has not changed in the last few years (1), even with the addition of two new drugs, aflibercept and regorafenib.

The study by Nanashima *et al.* (2) reported in this month's journal used old drugs, FU or CPT via the hepatic artery on 36 patients with colorectal liver metastases, 16 of whom had progressed after liver resection. Four of the patients had a complete response, 19 a partial response, for a total response rate of 64%. The median survival was 32 months, with the complete responders having a median survival of 62 months. Although, this is a small study and therefore difficult to make firm interpretations, the authors did have an interesting point, which is that by using old relatively inexpensive drugs, they were able to get a similar response and survival as seen in studies using new agents, which are quite expensive. Nanashima (2) stated that the cost of treating patients in Euros with arterial injections with 5FU or CPT was 3,590 Euros, while it was 75,534 Euros when Folfox treatment was used. This of course doesn't consider the extra cost that would be required if targeted agents were used. In an English study (3) when the cost of hepatic arterial infusion (HAI) therapy using a pump inserted at laparotomy was compared to systemic 5-FU/LV, the cost was more, but HAI therapy was more cost effective than systemic, when health care plus societal cost per life-year gained were considered. In an American randomized study (4) of HAI *vs.* Systemic, four quality of life end points were assessed. The study demonstrated that at 3 and 6 months the physical functioning was significantly improved for the HAI patients.

The goal of regional therapy is to increase therapeutic efficacy by increasing local concentration of the drugs and decreasing systemic exposure. Increased local concentrations depend on the ratio of total body clearance and the regional exchange for a particular body compartment (5). FUDR is the best drug for HAI because it has a short half life and a 94-99% first pass hepatic extraction. Drugs with high hepatic extraction (6) result in decreased systemic exposure. Prolonged exposure to FUDR in human cell lines greatly enhances its tumor inhibition (7). Nanashima *et al.* suggest that HAI- 5-FU or HAI-CPT may be better than HAI-FUDR, since their response rate was so high. Although the response rate was high in Nanashima' study, investigators have found a 400 fold increase in tumor exposure using HAI-FUDR and only a 40-fold advantage with 5-FU (8). With 5-FU the extraction ratio may differ according to the mode of administration with a 11% extraction rate with using usual administration but a 93% extraction rate with a 5-day infusion (9). Also, as the doses of 5-FU are increased the extraction rate decreases (10). HAI-CPT-11 seems to be not as effective as 5-FU or FUDR. With HAI-CPT there are increased systemic levels of SN-38 (which is the active metabolite) and lower levels of CPT compared to systemic CPT (11). This increase in SN-38 with HAI-CPT may be due to the high carboxyl esterase content in the liver (12). A Phase II study showed low a partial response rate with HAI-CPT though toxicity was similar to systemic CPT (11). With Oxaliplatin, there is a steep dose response curve in human colon cancer cells. Oxaliplatin is a prodrug and the cytotoxic activity of oxaliplatin is initiated by formation of a DNA adducts. A liver extraction ratio of 0.47 for oxaliplatin has been determined (13).

To perform HAI therapy a catheter has to be placed to allow perfusion of the liver via the hepatic artery. These catheters can be connected to ports or to pumps. The ports can be placed by interventional radiology, while the

pumps are usually placed by surgeons (14). The advantage to pumps is the ability of the pumps to remain patent, so there is continuous flow through the catheter, and one can deliver more cycles of chemotherapy. In one of the early randomized studies from England looking at HAI *vs.* systemic using a port, there were a lot of problems related to catheters and ports, so that 39% of patients were not able to receive HAI therapy (15). The study reported on the survival of all patients entered which included the 39% in HAI group who did not receive treatment and stated HAI did not improve results. They did not give the survival on the patients who actually got HAI therapy. In the CALGB study, the investigators used a pump -which allows continuous flow into the perfused artery and therefore less thrombosis of the artery. Thus, 80% of patients were able to receive treatment in the HAI group. In the CALGB randomized study, there was an increase in overall survival, hepatic progression-free survival and response rate with the HAI-FUDR + dexamethasone *vs.* systemic 5-FU/LV (4). Nanashima *et al.* (2) reported fewer problems maintaining their ports, and they also mentioned that as a working team gets familiar with HAI treatment, issues with catheters becomes less frequent, or often can be fixed.

The significance of HAI should be not only whether it is better than systemic, but also that it can be used with systemic therapy. When using drugs such as FUDR there is no systemic toxicity because there is a 95% extraction rate, so almost full doses of systemic therapy can be combined with the HAI therapy, allowing for more drug to actually be seen by the tumor. This allows for a higher response rate, which could possibly translate into a higher resection rate for patients with unresectable disease. In an MSKCC study on patients with unresectable liver metastases, 57% of chemo naive patients and 43% of previously treated patients were able to go on to liver resection after HAI and systemic therapy (16).

How do we move forward? One of the problems of funding studies looking at HAI therapy is that drugs such as 5-FU and FUDR are no longer made by drug companies; therefore, there is no support for testing them. The port and catheter companies don't seem to be interested in funding studies to show that hepatic arterial therapy may be better than systemic therapy and less expensive. There needs to be studies funded by governmental agencies to compare effective treatments, but also include cost analysis. If HAI therapies produce better results and are less costly, they certainly can be part of our therapeutic armamentarium to take care of colorectal patients in the future.

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