Editorial

Hype and hope of hepatic arterial infusion for colorectal cancer

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Contrary to most solid metastatic cancers, metastatic colorectal cancer could be cured by surgical removal of the metastasis in the context of lung or liver metastases. Large retrospective studies performed 20 years ago showed that surgery alone led to cure of the patient in about 35% of cases (1). To improve patient survival and to increase the cure rate, perioperative intravenous chemotherapy was proposed. In a large EORTC trial among highly selected patients, perioperative FOLFOX regimen improved relapse-free survival with an absolute difference in 3-year PFS of 8.1% (28.1% in the surgery-only group *vs.* 36.2% in the perioperative chemotherapy group) and there was a non-significant increase in overall survival (5-year overall survival was 51.2% in the perioperative chemotherapy group *vs.* 47.8% in the surgery-only group) (2). Despite this somewhat disappointing result, perioperative FOLFOX regimen became the standard of care for the management of resectable colorectal liver metastasis.

In the search to better stratify the risk of relapse, many clinical and pathologic factors, such as carcinoembryonic antigen, node positivity for the primary tumor, size and number of lesions, time interval between primary resection and the diagnosis of metastases, have been reported to predict the recurrence rate. Rat sarcoma viral oncogene homolog (RAS) mutations are detected in around 40% of colorectal cancers. RAS mutations are factors of resistance to anti EGFR therapies, and are associated with poor prognosis in the adjuvant and metastatic settings. Not surprisingly, the presence of RAS mutations has been associated with poor outcome, with reported 3-year overall survival rates of 81% *vs.* 52.2%, and 3-year recurrence-free survival rates of 33.5% *vs.* 13.5% for wild-type *vs.* mutant RAS tumors in the setting of liver metastasis surgery (3).

Because liver recurrence occurs in 50% of cases after liver metastasis surgery, it seemed logical to hypothesize that an increase in chemotherapy delivery to the liver might improve eradication of micro metastatic liver disease. Metastases in the range of 2 to 3 mm are not detectable, but could be responsible for liver relapse. Once a metastatic site exceeds 1 mm in size, hepatic metastases derive their blood supply from the hepatic artery, while normal hepatocytes are perfused mostly from the portal circulation. Therefore, adjuvant chemotherapy via the arterial circulation should logically increase drug delivery to undetectable liver metastasis. In the setting of colorectal cancer resistant to conventional chemotherapy, Hepatic Arterial infusion (HAI) using floxuridine yielded high response rates in multithreaded patients (4). Oxaliplatin can also be given by HAI and has shown considerable efficacy in association with intravenous perfusion of fluoropyrimidine or intraarterial infusion of raltitrexed (5,6).

In a retrospective analysis generated from the MSKCC database of patients treated by surgery for liver metastases of colorectal cancer, Gholami *et al.* (7) report the follow up of 674 patients with known KRAS status [418 KRAS wild-type (WT), 256 KRAS-mutation (MUT)]. Fifty-four percent received HAI chemotherapy, in the adjuvant setting for the majority. Patients treated with adjuvant HAI and systemic therapy had a lower initial recurrence rate involving the liver than patients treated with adjuvant systemic therapy

only (28.4% *vs.* 35.8%, P<0.04). Five-year relapse free survival (RFS) for patients with KRAS-WT was 33% (38% for patients treated with HAI plus systemic chemotherapy and 29% for patients treated with systemic chemotherapy only). For patients with KRAS-Mutant tumor, 5-year RFS was 23% (29% for patients treated with HAI plus systemic chemotherapy *vs.* 18% for patients treated with systemic chemotherapy only). Five-year OS for patients with KRAS-WT was 69% (73% *vs.* 63% for patients treated with HAI plus systemic chemotherapy *vs.* systemic chemotherapy alone) and 50% in KRAS-Mutated patients (57% for patients treated with HAI plus systemic chemotherapy *vs.* 43% for patients treated with systemic chemotherapy only). These data support the rationale that HAI given with systemic chemotherapy is efficient in enhancing RFS and OS, in both RAS wild-type and mutated tumors. This evidence also supports the use of HAI as a means to limit the poor prognosis of RAS mutated tumors.

Despite the impressive results reported from this retrospective single-centre study, caution is still warranted before the use of adjuvant HAI procedures. Only one old randomized clinical trial with small number of patients compared HAI with floxuridine *vs.* no adjuvant therapy. This study showed improved RFS, with no significant improvement in OS (8). The benefit is not very impressive in comparison with FOLFOX systemic adjuvant therapy, while the procedure is complex with a major risk of complication. Likewise, a recent Japanese phase III clinical trial failed to demonstrate the superiority of adjuvant HAI in comparison with intravenous chemotherapy, and reported substantial complication rates due to the procedure (9). Thus, based on current randomized clinical trials, adjuvant HAI should not be considered as a standard of care. Some ongoing clinical trials are currently addressing this question using different types of HAI procedure (NCT02494973, NCT02494973).

A major problem with the use of the HAI procedure after liver metastasis resection is extrahepatic relapse. Notably, lung recurrence occurs in around 50% of patients treated by liver metastasis resection (10). The presence of KRAS mutations was associated with an increased incidence of recurrence in the lung, bone and brain compared to wild-type patients (10), thus suggesting that the main issue in such tumors is not liver recurrence, but rather, systemic disease. With the development of triplet chemotherapy (11), which demonstrated a high rate of efficacy in metastatic disease in first line treatment, and the discovery that immunotherapy could be effective in the neoadjuvant setting for localized microsatellite stable colorectal cancer (12), there is reason to suspect that these therapies may take place and supplanted HAI in the setting of management of colorectal liver metastases.

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