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Review

Modern insights into hepatic arterial infusion for liver metastases from colorectal cancer

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ABSTRACT

Hepatic arterial infusion (HAI) selectively achieves high drug exposure of liver metastases from colorectal cancer. Such pharmacologic advantage has doubled the response rate of liver metastases on fluoropyrimidines (FP) delivered as HAI rather than intravenously, in a meta-analysis of randomised clinical trials (RCT). However, the improvement in antitumour efficacy did not consistently translate into any significant survival advantage across all randomised studies. However, the results of this meta-analysis should be cautiously interpreted due to the heterogeneity of the studies, inadequate study designs, obsolete therapy and high rate of early treatment discontinuation due to HAI technical failures or hepato-biliary toxicity. Most studies actually were performed before year 2000 and did not integrate the considerable progresses accomplished in the management of CRC, such as multidrug regimens instead of single agent FP and secondary resection of metastases, a major contributing factor for prolonged survival. Furthermore, the systemic exposure of patients given HAI was low without concomitant IV therapy, facilitating extra-hepatic relapses. The role of HAI in liver metastases from CRC should, therefore, be revisited, using modern multidisciplinary therapeutic approaches and appropriate study designs. Recommendations for the design of future RCTs exploring HAI are provided.

1. Introduction

Metastases are confined to the liver in 30–60% of the patients with metastatic colorectal cancer (mCRC).[1,2] Uncontrolled growth of hepatic metastases is fatal in patients with predominant liver metastases. Thus, most patients whose metastases are not resected die within 5 years of metastatic disease onset.[3,4] Complete surgical resection of metastases is, therefore, the only curative treatment for these patients.[4] Systemic chemotherapy is the standard of care that prolongs overall survival in patients with unresectable metastatic disease. Secondary resection after downstaging of initially unresectable metastases with systemic chemotherapy plays an important role in life prolongation and remains potentially curative.[5] It is, therefore, a primary objective of therapy in fit patients with mCRC.

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Hepatic arterial infusion (HAI) has been an appealing investigational method over the last 3 decades for patients with mCRC confined to the liver, in whom it has reproducibly yielded higher response rates than IV therapy. HAI offers theoretical advantages over standard intravenous (IV) administration of drugs. However, all randomised trials assessing this technique, using fluoropyrimidine (FP) alone, have not consistently improved survival outcomes.[6] Nevertheless the benefit of HAI, which is still giving raise to passionate debates,[7–9] should be revisited in the current era of multiple-drug armamentarium and multidisciplinary strategy against mCRC.

2. Why HAI should work?

Like any locoregional therapy, HAI provides high drug exposure of the tumour at first passage, capable of overcoming some drug resistance mechanisms, such as drug efflux. However, to be clinically relevant, therapy with HAI should preferentially expose tumour cells to high drug concentrations, while both extra-hepatic tissues and healthy hepatocytes are relatively protected.

2.1. *Metastatic spread peculiarity of CRC*

Necropsy studies have shown that liver deposits are a compulsory first visceral step in the metastatic spread of CRC.[2,3,10] Hence there is a therapeutic slot in the CRC natural history, when metastatic disease is still confined to the liver and the disease still at a locoregional stage. This explains why complete resection of liver metastases may be curative, even in the absence of any systemic therapy, when it is performed before further metastatic spread beyond the liver has occurred. Thus, when isolated liver metastases are not resectable, HAI administration of drugs is a logical method of locoregional disease control. Furthermore, even when the disease has spread beyond the liver, e.g. small lung deposits coexisting with large hepatic metastases, the patient's life is immediately threatened by metastatic progression in the liver. Thus, effective locoregional hepatic therapy theoretically could still prolong survival.

2.2. *Anatomic opportunity*

While newly arising, microscopic liver metastases, as well as normal liver, are preferentially irrigated by the portal venous blood flow, established macroscopic metastases are preferentially fed by the hepatic arterial blood supply.[11,12] Delivering drugs via the hepatic artery results in a higher exposure of, and a higher drug clearance by, tumour cells, compared to normal hepatocytes and, consequently, yields a more selective killing of cancer cells.

2.3. *Pharmacological condition: Drugs with high hepatic clearance*

Drugs to be used via HAI should have a high first-passage hepatic clearance, responsible for a low systemic exposure allowing for dose increment and even higher local exposure.[13] In this respect, floxuridine (FUDR), a prodrug of fluorouracil (5-FU) with a hepatic extraction rate >90% that results in a hepatic/systemic ratio of 100–400 is more suitable for HAI than 5-FU with a hepatic extraction rate <50% and a hepatic/systemic ratio around 10.[7] Similarly, Munck et al. reported very elegant results with pirarubicin (P), a doxorubicin analogue with a much higher cellular uptake than the parent compound.[14] In a rabbit VX2 tumour model, they showed that HAI administration of P resulted in intra-tumour drug concentration 10-fold higher than IV administration, while HAI doxorubicin resulted in intra-tumour concentration only twice that achieved with the IV route. Furthermore, systemic exposure after HAI P, including heart exposure, was much lower than after IV P, HAI or IV doxorubicin. Similar results were reported in the same animal model with oxaliplatin, compared to cisplatin.[15] HAI of oxaliplatin achieved higher tissue concentrations than IV oxaliplatin, HAI or IV cisplatin.

3. Proof of concept

Randomised clinical studies comparing HAI to IV FP have consistently shown a significantly higher response rate with the HAI route. In the meta-analysis of all published randomised trials, the response rate was 42.9% with HAI, versus 18.4% with the IV route. Achieving a response was 2.26-fold more likely with HAI than with IV infusion ($p < 0.0001$).[6,7] This major difference shown in these old studies offers a proof of principle that the theoretical advantages of the HAI route actually translate into a higher clinical activity of fluoropyrimidines.

An advantage in terms of overall survival was shown in only three studies of the meta-analysis.[16–18] This advantage should be interpreted cautiously for the two oldest trials, because many patients in the control arm did not receive systemic chemotherapy. In turn, in the most recent CALGB trial,[18] all patients of the control arm were given systemic chemotherapy and the survival advantage observed is an important argument in favour of HAI.

In clinical studies testing HAI pirarubicin in patients with mCRC to the liver,[19–21] response rates >30% were reported, which are impressive considering the well-established resistance of CRC cells to anthracyclines. In addition the authors confirmed a 4-fold decrease in systemic exposure to P given via the HAI route compared to the IV route in humans. P-glycoprotein-driven drug efflux is probably the clinically predominant mechanism of anthracycline resistance.[22] Clinical responses concomitant to high drug concentration within tumour cells is, therefore, consistent with drug resistance reversal due to drug efflux pump saturation. In the pirarubicin model, clinical data have, therefore, confirmed the relevance of the findings established in animal models.

4. Why has the benefit of HAI not been clearly demonstrated so far?

Despite the accumulation of clues of clinically meaningful activity, HAI of drugs has not been validated yet as a standard therapy in mCRC. In 1996 a first meta-analysis including the first six published randomised studies testing HAI concluded