

Intrahepatic therapy for liver-dominant metastatic colorectal cancer

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Author contributions: De Groote K and Prenen H contributed equally to this work.

Conflict-of-interest statement: No conflict of interest.

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Received: March 21, 2015

Peer-review started: March 22, 2015

First decision: July 1, 2015

Revised: July 6, 2015

Accepted: July 29, 2015

Article in press: August 3, 2015

Published online: September 15, 2015

Abstract

In patients with metastatic colorectal cancer, the liver is the most common site of metastatic disease. In patients with liver-dominant disease, consideration needs to be given to locoregional treatments such as hepatic arterial infusion chemotherapy, transarterial chemoembolisation and selective internal radiation therapy because hepatic metastases are a major cause of liver failure especially in chemorefractory disease. In this review we provide

insights on the published literature for locoregional treatment of liver metastases in metastatic colorectal cancer.

Key words: Colorectal cancer; Liver metastases; Intrahepatic treatment; Chemoembolization; Radioembolisation

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Core tip: Thanks to the increased chemotherapeutic options in patients with metastatic colorectal cancer (mCRC), the overall survival has significantly improved the last decade. Liver failure is a common cause of death in mCRC with liver metastases. Therefore in these patients locoregional treatment is a valuable treatment option in order to increase survival. In this review we provide insights on the published literature.

De Groote K, Prenen H. Intrahepatic therapy for liver-dominant metastatic colorectal cancer. *World J Gastrointest Oncol* 2015; 7(9): 148-152 Available from: URL: <http://www.wjgnet.com/1948-5204/full/v7/i9/148.htm> DOI: <http://dx.doi.org/10.4251/wjgo.v7.i9.148>

INTRODUCTION

Although the incidence and the mortality of colorectal cancer (CRC) have decreased over the years in some countries, it still remains one of the most prevalent and the third leading cause of cancer death worldwide^[1]. Even with improved screening, the incidence of synchronous and metachronous disease remains high. Approximately half of patients with CRC will develop liver metastases^[2]. When mCRC is treated with a combination of chemotherapy (5-FU, oxaliplatin, irinotecan) and targeted agents such as the anti-epidermal growth factor receptor and anti-vascular growth factor

monoclonal antibodies, median overall survivals now extend beyond 24 mo in the clinical trial setting^[3]. Hepatic metastases are a major cause of liver failure especially once all chemotherapeutic and/or surgical options have been exhausted. Although surgical resection of liver metastases for curative intent is the treatment of choice, most patients present with unresectable liver-predominant metastatic CRC (mCRC). In these cases, consideration needs to be given to the (often favorable) efficacy and safety of locoregional treatments such as hepatic arterial infusion (HAI) chemotherapy, transarterial chemoembolization (TACE) and selective internal radiation therapy (SIRT), either alone or in combination with systemic chemotherapy.

In this review, we provide further insights on the published literature for the locoregional treatment of liver metastases in patients with mCRC.

HEPATIC INTRA-ARTERIAL CHEMOTHERAPY

There is a compelling argument for HAI chemotherapy in patients with liver-predominant mCRC because of the preferential perfusion of liver metastases (compared with the normal parenchyma) by the hepatic arterial network whereas non tumor liver parenchyma is preferentially perfused by the portal vein. In addition, local intra-arterial treatment circumvents the first-pass effects of the liver, exposing the liver metastases to high concentrations of chemotherapy while at the same time reducing the incidence of unwanted systemic side effects.

The femoral artery is the most common access route. The catheter tip is placed into the hepatic artery at the junction of the gastro-duodenal artery to enable bilobar hepatic infusion. To avoid gastric or duodenal lesions, selective distal embolization is performed of the side branches of the hepatic artery leading to the adjacent organs. Catheter displacement or occlusion remains the most frequently reported complication of HAI chemotherapy use^[4].

In the United States, fluorodeoxyuridine (FUDR), a 5-FU derivative, is the most commonly used chemotherapy agent in patients treated with HAI chemotherapy. FUDR has the advantage of being rapidly metabolized, with a 94%-99% extraction rate within the liver *via* first-pass metabolism, so enabling high intrahepatic concentrations when given by HAI, but the downside of this HAI chemotherapy is hepato-biliary toxicity which may lead to biliary sclerosis. However, when combined with dexamethasone (Dex), the toxicity of HAI FUDR toxicity is reduced^[5]. In Europe, 5-FU is more frequently used which has only a 50% extraction rate in the liver, but systemic blood concentrations of 5-FU are higher than FUDR, making it a more effective against extra-hepatic (micro)metastases. 5-FU is also less hepatotoxic compared with FUDR. Oxaliplatin and irinotecan, the other chemotherapeutic agents active in CRC are

also now more commonly used for HAI; although the available data are scant^[6-8].

Although its rationale is appealing, the benefit of HAI chemotherapy is unclear because of the lack of large randomized trials. Chemotherapy can be used either as neo-adjuvant therapy for isolated, potentially resectable CRC liver metastases or as adjuvant therapy after complete resection in patients at high-risk of recurrence. In the neo-adjuvant setting, the aim of chemotherapy is to render unresectable liver metastases resectable. It is recognized that classical chemotherapy schedules in combination with monoclonal antibodies can achieve response rates up to 80%^[9] but the optimal HAI chemotherapy regimen has yet to be established. In the absence of large phase III trials, evidence for the reported improvements in resectability with HAIC in CRC-related inoperable liver metastases is based solely on small phase II studies^[6,7,10]. In the adjuvant setting after curative hepatectomy, phase II studies also provide evidence for lower recurrence rates when HAI chemotherapy is combined with systemic chemotherapy^[11,12]; thereby providing proof-of concept but evidence from large phase III trials are still needed.

In inoperable liver-only mCRC, HAI chemotherapy might also be used to achieve locoregional control. A study conducted by the Medical Research Council and the European Organization for the Research and Treatment of Cancer, randomly assigned 290 patients with unresectable CRC liver metastases to either HIA with 5-FU and leucovorin (LV) or systemic 5-FU/LV. The study observed no difference between the treatment arms for overall survival (OS) (14.7 mo vs 14.8 mo), progression-free survival (PFS) or toxicity^[13]. There was, however, a high frequency of catheter-related thrombosis in the HAI chemotherapy arm (36%) resulting a lower proportion of patients receiving the intended six or more chemotherapy cycles compared with systemic chemotherapy (38% vs 75%)^[13]. Some patients in this trial crossed-over to intravenous chemotherapy, but were still analyzed as HAI in an intention-to-treat manner, thereby making it difficult to draw any definitive conclusions from this trial. In contrast, another study lead by the Cancer and Leukemia Group B (CALGB) randomly assigned 135 patients with inoperable CRC liver metastases to either HAI-FUDR/LV/Dex or systemic 5-FU/LV and observed a significant benefit in favor of HAI for both median OS (24.4 mo vs 20 mo, $P = 0.0034$) and response rate (47% vs 24%; $P = 0.12$)^[14]. There was no significant difference in time to progression (TTP) (5.3 mo vs 6.8 mo), but the time to hepatic progression was longer in the HAI group (9.8 mo vs 7.3 mo), and time to extra-hepatic progression was longer in the systemic group (14.8 mo vs 7.7 mo)^[14].

More recent studies have also evaluated oxaliplatin and irinotecan for HAI. In a French phase II study, 26 patients with inoperable, liver-only mCRC were treated with a combination of HAI-oxaliplatin plus systemic

5FU/LV^[6]. Twenty-one patients had been pretreated with one line of 5-FU-based therapy, none had previously received oxaliplatin. The median OS was 27 mo, and response rate reported was 64%, which were comparable to regimens with HAI-FUDR and systemic 5FU-LV. In a second study of HAI-FUDR plus systemic 5FU/LV, the same research group investigated patients who had received more than one line of systemic chemotherapy: either FOLFIRI or FOLFOX or both (percentage of 86%, 77% and 96% respectively). The median OS was 16 mo, response rate 62% (18% down-staged for resection) and median PFS 7 mo. Although the results of these studies are initially promising, the advantage of this approach still needs to be confirmed in a phase III study vs systemic chemotherapy alone.

TRANSARTERIAL (CHEMO)EMBOLIZATION

TACE, the combination of the injection of a drug and embolic material, has mostly been used in hypervascular tumors such as hepatocellular carcinoma. The use of drug-eluting beads (DEB) enables the controlled release of drug after the beads are trapped in the tumoral circulation. Modern angiographic techniques make it possible to selectively deliver the material to the tumor resulting in minimal release of cytotoxic agent(s) into the surrounding tissues.

In mCRC, different chemotherapeutic agents can be used to load the drug eluting beads. A prospective single-center study evaluated 463 patients with chemorefractory, unresectable CRC liver metastases who were treated with TACE at 4-wk intervals^[15]. Three TACE regimens were used, either: mitomycin C alone, mitomycin C with gemcitabine, or mitomycin C with irinotecan. Embolization was performed with lipiodol and starch microspheres. A total of 2441 TACE procedures were performed (mean of 5.3 sessions per patient). The median OS in this chemorefractory population was 14 mo, with no significant difference between the different chemotherapy protocols. Disease control was 62.9% [14.7% partial response (PR), 48.3% stable disease (SD)]^[15]. Another German study also evaluated retrospectively the same chemotherapy schedules in 564 patients in either the neoadjuvant or palliative setting^[16]. Like the previous study, no significant differences in OS were observed between the chemotherapy regimens and response rates were also in the same range (16.7% PR, 48.2% SD). Finally disease control rates of 43% were found in another retrospective analysis of 121 patients in the chemorefractory setting with TACE with cisplatin, doxorubicine and mitomycin C^[17].

To date, the published experience with chemoembolization using DEB-irinotecan (DEBIRI) has mostly been performed in liver-predominant CRC. DEBIRI was evaluated in a phase II study in 82 chemorefractory liver-predominant CRC patients, resulting in very high response rates of 78% at 3 mo post-treatment and

a mean PFS of 8 mo^[18]. In another study response rates with DEBIRI were 66% and 75% at 6 and 12 mo, respectively and PFS was 11 mo^[19]. In both these studies of DEBIRI, the most common adverse event was post-embolization syndrome reported as abdominal pain, nausea and vomiting^[18,19]. Usually symptoms were mild and transient; rarely has there been any reports of liver toxicity associated with liver abscess, liver failure or pancreatitis and only when more extensive embolization was performed.

Pharmacokinetic studies evaluating DEBIRI show that plasma levels of irinotecan and its active agent SN-38 were almost undetectable 24 h after administration^[20]. Only one small randomized phase III study has been performed comparing DEBIRI with systemic chemotherapy (FOLFIRI)^[21] in 74 patients with unresectable mCRC without extrahepatic disease, who were refractory to at least two lines of chemotherapy. A survival advantage with DEBIRI was suggested (median OS of 22 mo vs 15 mo with FOLFIRI; $P = 0.031$). The DEBIRI group also had a significantly higher objective response rate (69% vs 20%)^[21].

In conclusion, several studies suggest that TACE can achieve disease stabilization in 40%-60% of patients, but whether this leads to a prolongation of OS relative to systemic chemotherapy is uncertain, since almost no randomized-controlled trials have been performed. Therefore larger randomized trials are needed for comparison with standard intravenous chemotherapy.

SELECTIVE INTERNAL RADIATION THERAPY

Selective internal radiation therapy (SIRT) (or radioembolization) is a form of intra-arterial brachytherapy using resin-based microspheres impregnated with ⁹⁰Yttrium (⁹⁰Y) as the radiation source. SIRT using ⁹⁰Y resin microspheres was approved by the FDA in 2002. ⁹⁰Y-resin microspheres are delivered into the tumor-feeding arteries of the hepatic arterial circulation and embed permanently in the pre-capillary arterioles of liver tumors where they deliver very high doses of localized radiation (and so minimizing the damage to the healthy liver parenchyma). In general, SIRT is safe and well tolerated with fewer side effects and milder post-embolization syndrome than with observed TACE. However, SIRT is more complex to administer and therefore its use is often restricted to specialized centers. Specific complications are rare, and include gastroduodenal ulceration, pancreatitis, cholecystitis, abscess formation and radiation-induced liver or lung disease.

Approval was based on one randomized controlled trial in which 74 patients with liver isolated CRC metastases were assigned to either HAI-FUDR alone or HAI-FUDR in conjunction with a single administration of SIRT^[22]. The study found that compared with HAI, the combination of SIRT and FUDR-HAI led to a significantly better complete response rates (44% vs 18%) and

prolonged the median time to progression (16 mo vs 10 mo).

Radioembolization has also been compared to intravenous chemotherapy in two prospective randomized-controlled trials^[23,24]. The first RCT was a small phase II study conducted by Van Hazel *et al.*^[23] in 21 patients with previously untreated liver-predominant mCRC. Systemic 5-FU/LV preceded by a single SIRT procedure significantly prolonged median OS (29.4 mo vs 12.8 mo) as well as time to progression (TTP) (18.6 mo vs 3.6 mo) compared with 5FU/LV alone. More recently, a phase III study assigned 44 patients with chemotherapy refractory liver-limited metastatic CRC to treatment with 5-FU monotherapy or SIRT during the first cycle of chemotherapy followed by 5-FU monotherapy, until hepatic progression^[24]. Cross-over to SIRT was permitted after progression in the 5-FU monotherapy arm. Once again the combination of SIRT and systemic chemotherapy significantly improved TTP (4.5 mo vs 2.1 mo), but without any difference in OS between the two arms (10.0 mo vs 7.3 mo) primarily due to the cross-over of some patients from 5-FU monotherapy to the SIRT arm following progression studies in which SIRT is added to more modern systemic chemotherapy such as FOLFOX and bevacizumab (SIRFLOX and FOXFIRE study) are now ongoing with initial results from SIRFLOX likely to be presented in 2015.

To date most of the published studies with SIRT are in chemorefractory liver predominant mCRC. A systematic review of twenty studies comprising 979 patients treated with ⁹⁰Y-resin microspheres revealed a median time to intrahepatic progression of 9 mo and OS of 12 mo^[25]. Although this review has several shortcomings such as: the inclusion of multiple observational studies, studies with small sample sizes and the heterogeneity of patients, it still demonstrated that SIRT was safe and an effective treatment for unresectable, chemorefractory mCRC.

CONCLUSION

The management of chemorefractory liver metastases from mCRC is a major challenge and effective treatment options are urgently needed. Both HAI chemotherapy as well as TACE and SIRT appear to be effective in this setting when used in centers with expertise in the technical aspects of these local treatments. However, adequately powered prospective phase III studies are still needed. Landmark studies such as SIRFLOX and FOXFIRE with SIRT are expected to help better define the role of these treatments earlier in the course of liver-predominant mCRC.

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P- Reviewer: Sertoglu E **S- Editor:** Ji FF **L- Editor:** A
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