Bull Cancer 2016; □□: □□□

en ligne sur / *on line on*
www.em-consulte.com/revue/bulcan
www.sciencedirect.com

Review

Intra-arterial therapies for colorectal cancer liver metastases (radioembolization excluded)

Thierry de Baere [1,2], Lambros Tselikas [1,2], Valérie Boige [1,2], Michel Ducreux [1,2], David Malka [1,2], Diane Goéré [1,2], Eléonore Benahim [1,2], Frédéric Deschamps [1,2]

Received 21 October 2016
Accepted 29 October 2016
Available online:

1. Gustave-Roussy Cancer Center, Department of Interventional Radiology, 114, rue Edouard-Vaillant, 94805 Villejuif, France
2. Université Paris-Sud XI, UFR Médecine, 94270 Le Kremlin-Bicêtre, France

Correspondence:
Thierry de Baere, Gustave-Roussy Cancer Center, Department of Interventional Radiology, 114, rue Edouard-Vaillant, 94805 Villejuif, France.
thierry.debaere@gustaveroussy.fr

Keywords
Colorectal cancer
Liver metastases
Local treatment
Hepatic arterial infusion chemotherapy
Transarterial chemoembolization

Summary

During the past 20 years, advances in systemic therapies have improved overall survival of patients with Colorectal cancer Liver metastases (CRLM) from 6 to 24 months. By reaching CRLM via their preferential arterial vascularization, hepatic arterial infusion of chemotherapy (HAIC) has demonstrated improvement in response rate and deepness of response. Improvement in deepness of response is potentially helpful to convert no surgical patient to surgery. Recent HAIC regimens, including HAIC-FUDR plus systemic oxaliplatin/irinotecan, or HAIC-oxaliplatin plus systemic 5FU and cetuximab yielded a 92% and 90% response rate respectively, and conversion to R0 surgery in 47% and 42% of patients, respectively. When HAIC delivered a drug ineffective through intravenous delivery, this rechallenge provided 62% response rate for HAIC. Nowadays, port-catheter implanted percutaneously by radiologists has 95% feasibility with primary patency equivalent to that of surgically implanted catheters, and secondary patency superior after radiologic revision. Retrospective studies demonstrated prolonged DFS of HAIC over IV chemotherapy in the adjuvant setting after surgery of CRLM. Drug eluting beads loaded with irinotecan (DEBIRI) were developed as drug carrier and embolization platform for treatment of CRLM by chemoembolization. DEBIRI allows for a very high level of SN-38 (SN-38 is the active compound of irinotecan) and a very high rate of complete l response at pathologic studies of treated metastases. DEBIRI was compared to systemic FOLFIRI in a phase III randomized trial including 74 patients with benefit in overall survival and disease-free survival.

http://dx.doi.org/10.1016/j.bulcan.2016.10.025

To cite this article: de Baere T, et al. Intra-arterial therapies for colorectal cancer liver metastases (radioembolization excluded). Bull Cancer (2016), http://dx.doi.org/10.1016/j.bulcan.2016.10.025

Colorectal liver metastases (CRLM) will occur in 50 to 75% of patients with know colorectal cancer, and CRLM is the most common cause of death from this cancer. Surgery is the best treatment option for CRLM, with 5-year OS rates around 50% [1], but surgery is possible upfront in only 20% of patients. For nonsurgical candidates, the median survival of patients with colorectal liver metastases was 10–14 months when treated with 5FU and leucovorin [2]. This survival increased to 16.2 and 14.8 months when adding oxaliplatin or irinotecan respectively [3]. Most recent chemotherapeutic regimens, including combination with EGFR and VEGF inhibitors, provide a median survival of up to 2 years [4], probably due to conversion of non-operable patient to surgical candidates. Trying to enhance benefit of chemotherapy, arterial therapies take advantage that the liver vascularization is 30% arterial and 70% portal, while tumor growing in the liver are nearly exclusively fed by the arterial blood [5], thus any compound injected in the hepatic artery will preferentially reach the tumor. Intra-arterial therapies encompassed hepatic arterial infusion of chemotherapy (HAIC), transarterial embolization (TAE), transarterial chemoembolization (TACE), radioembolization. Only TACE and HIAC are in the scope of this paper.

Hepatic artery infusion chemotherapy (HAIC)

HAIC has the goal of increasing drug concentrations in tumor deposits, thus resulting in a significant increase in response rates because many tumors display a steep dose–response curve. The advantage for such intra-arterial route is proportional to first pass extraction of the drug by the liver and inversely proportional to body clearance of the drug. Consequently, the choice of the drug is of major importance. FUDR because extracted by the liver at more than 95% during the first pass, results in an increase of exposure of the tumor by 100 to 300 folds when compared with systemic perfusion. The estimated increase in liver exposure by HAIC are about 20 fold for THP adryamicin, 5 to 10 fold for 5FU, 4 to 7 fold for cisplatin, 6 to 8 fold for mitomycine, 5 fold for oxaliplatinum, and only 2 fold for doxorubicin [6]. HAIC is delivered every second week, or using continuous infusion. In order to be able to achieve this repeated hepatic intra-arterial injection, a permanent and easy access to the hepatic artery is needed and implantation of a subcutaneous port or a pump linked to an intra-arterial catheter is the rule.

Catheter insertion

The unique route of catheter insertion until recently was by laparotomy with retrograde cannulation of the gastroduodenal artery. Percutaneous implantation is now a mature technique and provides equivalent or superior results to surgical implantation. The complete liver has to perfuse through a single artery, and this single artery must infuse chemotherapy to liver only. Infusion of chemotherapy in the complete liver through a single artery means proximal occlusion of additional replaced hepatic arteries with steel coils, when such arteries are present. Infusing chemotherapy to liver only implies occlusion of every single artery arising from the hepatic artery downstream of the infusion hole in the catheter when feeding neighboring organs (stomach, duodenum, pancreas…) [7,8]. The gastroduodenal artery (GDA) and the right gastric artery are nearly always requiring an endovascular occlusion because of the risk of acute gastric mucosal lesions [7,9]. Systematic occlusion of cystic artery is not needed. Most often, the indwelling catheter is inserted deeply in the GDA in sake of stability, with a perfusion side hole placed in the distal part of the common hepatic artery [7]. When gastroduodenal artery cannot be catheterized, does not exist or has been ligated, the tip of the indwelling catheter will be placed in a peripheral branch of the hepatic artery and the side hole is left in the hepatic artery proper as described in details elsewhere [7].

Success rates for the percutaneous femoral implantation is 94 to 99%, [7,8,10]. Comparisons of percutaneous and surgically placed port-catheter for HAIC report equivalent primary functionality (4.80 vs. 4.82 courses), with significantly higher secondary functionality for percutaneously placed port-catheters that allow for successful percutaneous revision (9.18 vs 5.95 courses, $P = 0.004$) [7,11]. Overall, the rates of discontinuation of HAIC linked to complications of the port-catheters system are 21% after percutaneous implantation and 34% after surgical placement [12], questioning surgical placement even when catheter is inserted during a surgery performed for other reasons [13].

Dysfunction that requires re-intervention includes 30% of extrahepatic perfusion and 3 to 10% catheter migration or occlusion. Regular controls of catheter function by imaging is recommended with digital subtracted angiography or scintigraphy. In the event of dysfunction percutaneous re-intervention should be attempted [14].

Results of HAIC

In the early 90s, many randomized control trials report significant improvement of tumor response with HAI 5FU or FUDR versus IV injection [6], although only few of these studies demonstrated a survival benefit for HAIC vs IV chemotherapy [15,16], due to cross-over allowed in most trials and low completion of HAIC. Recently, 68 patients with initially unresecable CRLM who had undergone hepatic resection after at least 6 cycles of oxaliplatin-based chemotherapy administered either via HAI ($n = 18$) or IV ($n = 50$) were studied for tumor response at pathologic examination [17]. HAI was associated with higher chance of complete pathologic response (OR: 9.33, 95% confidence interval: 1.59–54.7) but also higher risk of severe oxaliplatin-related lesions to liver parenchyma (OR: 13.7, 95%