Hepatic arterial infusion in colorectal carcinoma: is anatomical targeting still relevant in an era of molecularly targeted therapy?

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Background. Historically, metastatic colorectal carcinoma was regarded as a tumor that is relatively resistant to cytotoxic agents. Due to the limited number of treatment options, methods have been investigated to enhance selectivity. One method for enhancing selectivity is anatomical targeting, including hepatic arterial infusion (HAI).

Methods. A comprehensive review of the literature.

Results. Early studies with HAI used fluoropyrimidines, 5-fluorouracil or floxuridine. Several randomized trials comparing the HAI of fluoropyrimidines with systemic administration of fluoropyrimidines or best supportive care that were conducted in the 1980s and early 1990s demonstrated a superior objective response rate, but usually not a prolongation of survival in patients treated with HAI. The current standard of first line systemic chemotherapy of metastatic colorectal carcinoma is combination chemotherapy (fluoropyrimidines, oxaliplatin and/or irinotecan) administered with targeted agents. A number of trials have reported promising activity of the HAI of oxaliplatin and/or irinotecan with fluoropyrimidines, but only pilot studies are available for the combination of HAI of cytotoxic agents with targeted drugs. Factors that limit the effectiveness and utilization of HAI include catheter or port system-related complications, the presence of extrahepatic metastases, or increased risk of hepatic toxicity.

Conclusions. HAI could be considered in clinical practice in different settings, including patients after liver resection, as second line therapy in patients failing standard front line regimens and as neoadjuvant therapy to convert to resectability. Future studies should specifically concentrate on identifying regimens that would result in increased cure rates in patients with isolated hepatic metastases. For this reason, exploiting anatomical selectivity may still be a useful approach, even in the era of targeted therapy.

Key words: 5-fluorouracil, colorectal carcinoma, floxuridine, hepatic arterial infusion, irinotecan, oxaliplatin

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INTRODUCTION

Colorectal carcinoma is one of the most frequent malignant tumors and also one of the leading causes of cancer mortality. An overwhelming majority of colorectal carcinoma deaths are caused by uncontrolled growth of metastases. These metastases are either present at the time of diagnosis or develop later during the course of follow up. Surgery is the mainstay of therapy in localized colorectal carcinoma. However, in patients with metastatic disease the utilization of surgery is limited to a subgroup of patients with resectable (usually liver or lung) metastases, and even in this selected subgroup surgical resection is usually not curative.

Chemotherapy is the principal therapeutic modality in patients with metastatic colorectal carcinoma. Historically, colorectal carcinoma has been resistant to most cytotoxic agents. During the last 20 years, we have witnessed considerable progress in the chemotherapy of colorectal carcinoma. After demonstration that fluoropyrimidine-based chemotherapy significantly prolongs survival in patients with metastatic colorectal carcinoma^{1,2}, two new active agents, irinotecan and ox-

aliplatin, have been introduced, and further incremental survival gains have been demonstrated for the combination of fluoropyrimidines with these drugs^{3,4}, or, more recently, with targeted agents^{5,6}. Raltitrexed, a drug that, like fluoropyrimidines, acts through thymidylate synthase inhibition has also been registered for the therapy of metastatic colorectal carcinoma⁷. However, the utilization of raltitrexed has been largely abandoned due to unpredictable toxicity. Currently, five classes of drugs with different mechanism of action are registered for the therapy of metastatic colorectal carcinoma, including fluoropyrimidines (5-fluorouracil and its pro-drug capecitabine) as antimetabolites, topoisomerase I inhibitor irinotecan, platinum derivative oxaliplatin, anti-vascular endothelial growth factor (VEGF) antibody bevacizumab and the monoclonal antibodies targeting epidermal growth factor receptor (EGFR) cetuximab and panitumumab. Unfortunately, these agents or their combinations are rarely curative in the setting of metastatic disease. In almost all patients initially responding to the therapy, the disease will eventually progress necessitating therapy with non-cross resistant anticancer drugs. Even with the availability of more active agents, therapeutic options using agents

currently registered or their combinations usually become exhausted during the course of the disease. Therefore, new active drugs, e.g. patupilone⁸, or more effective methods of administration of the active agents already identified, e.g. hepatic arterial infusion (HAI) need to be explored.

The liver represents the most common site of distant metastases in general. The liver is also the most common site of metastatic disease in colorectal carcinoma⁹⁻¹¹. Moreover, the metastatic involvement of the liver is often isolated, i.e. without any extrahepatic metastases⁹. Distant metastases in colorectal cancer usually spread in a metastatic cascade, first affecting the liver, then spreading to the lungs, and only after lung involvement metastasizing to other organs⁹. This pattern of metastatic spread contrasts with other tumors, e.g. gastroesophageal or renal cell carcinomas¹²⁻¹⁵. Hepatic resection is currently the only curative therapy in patients with colorectal cancer liver metastases, but most patients with liver metastases present with non-resectable lesions, and these patients are treated by palliative chemotherapy. HAI of cytotoxic agents in patients with liver metastases has the advantage of higher intratumoral drug concentration and less systemic toxicity¹⁶. In patients with colorectal cancer metastatic to the liver, it has been demonstrated in clinical trials that these theoretical advantages translate into superior response rate and quality of life^{17,18}. It has, however, been more difficult to demonstrate an improvement in survival, and only recently, a survival advantage of HAI compared to systemic chemotherapy could be demonstrated¹⁹. Consequently, the use of HAI in colorectal cancer metastatic to the liver is controversial. The role of HAI in patients with liver metastases of other primary tumors is even less clear.

THEORETICAL FOUNDATIONS OF HAI

Given the dose-response effect that is evident for many cytotoxic agents, there is an obvious attempt to administer the maximum tolerated dose. Cytotoxic drugs have some degree of selectivity for transformed neoplastic cells, but always have some toxic effects on normal tissues as well. Thus, increasing the dose results not only in higher efficacy, but also more side effects. Ultimately, systemic toxicity limits further dose escalation. Owing to limited inherent selectivity of cytotoxic drugs, different approaches have been explored to increase selectivity by other manipulations. One such approach is to exploit anatomy to achieve selective drug delivery. In some instances the tumor spread involves only certain anatomical compartments that may be targeted selectively. The aim is to increase the drug concentration in the tumor microenvironment with lower systemic concentrations that would result in limited toxicity. The strategy of anatomical targeting may be used in cases of superficial tumor spread inside the peritoneal cavity, urinary bladder and meningeal space. Similarly, vascular structures may be used to target the tumor, e.g. in cases of tumors of the extremities or liver tumors. In addition, intraarterial administration may take advantage of the first-pass effect.

The pharmacokinetic advantage of intraarterial compared to systemic administration of a drug may be quantified²⁰. The increase of target drug concentration by regional compared to systemic administration may be expressed by the ratio:

$$R_{\text{target}} = C_{\text{target}} (\text{regional administration}) / C_{\text{target}} (\text{intravenous administration}),$$

whereas decreased systemic concentration may be expressed in a similar manner to:

$$R_{\text{systemic}} = C_{\text{systemic}} (\text{regional administration}) / C_{\text{systemic}} (\text{intravenous administration}) \text{ (ref. }^{20}\text{)}.$$

C denotes here the steady-state drug concentration in case of continuous infusion or area under the curve in case of bolus administrations.

The selectivity of regional administration (R_d) may be defined by the ratio:

$$R_d = R_{\text{target}} / R_{\text{systemic}}.$$

This ratio may be estimated by the following formula:

$$R_d = 1 + CL_{\text{TB}} / Q \times (1 - E),$$

where CL_{TB} is the total body clearance, Q is the regional exchange rate and E is the fraction extracted during the first pass²⁰.

HAI, intraarterial infusion via the hepatic artery, is the method of regional chemotherapy most commonly used. Normal liver parenchyma has a blood supply from both the portal vein and hepatic artery. Seeding of liver metastases occurs hematogenously via portal blood supply. While small tumors have blood supply from both portal vein and hepatic artery²¹⁻²³, with increasing tumor size the arterial supply prevails, and large tumors are supplied almost exclusively by the branches of the hepatic artery²¹⁻²⁴. Sigurdson et al.²⁵ compared hepatic and tumor floxuridine concentrations after HAI or portal vein infusion. While the drug concentrations were comparable in the liver, tumor floxuridine concentrations were more than an order of magnitude higher after HAI (ref.²⁵).

Since many cytotoxic drugs are metabolized in the liver, HAI takes advantage of the first-pass effect. The pharmacokinetic advantage is best defined for fluoropyrimidines, 5-fluorouracil, 5-fluoro-2'-deoxyuridine (floxuridine), and 5'-deoxy-5-fluorouridine (doxifluridine). 5-fluorouracil and floxuridine were available since 1950s (ref.²⁶). The synthesis of doxifluridine was first reported by Hřebáček and Beránek in 1978 (ref.²⁷), but this drug has mostly been used in Eastern Asia. The pharmacokinetics of HAI of 5-fluorouracil and floxuridine has been extensively studied²⁸⁻³¹. The hepatic extraction ratio and clearance is significantly higher for floxuridine than for 5-fluorouracil²⁹.

The effectiveness of HAI may be limited by the presence of arterial-venous shunts that may be detected by sorbitol clearance. It has been observed that the systemic toxicity of HAI is higher in patients with arterial-venous shunts³². Attempts have been made to harness therapeutically the absence of continuous smooth muscle layer and autonomic innervations in tumor blood vessels compared to normal arteries³³, but the results of clinical studies have been disappointing^{34,35}. It remains to be determined whether this difference between normal and tumor blood vessels could be exploited in combinations of HAI and targeted agents.

HAI results in higher drug concentrations and efficacy only in tumors supplied by the hepatic artery. Drug concen-

trations and efficacy in extrahepatic tumors is usually lower when the drug is administered as HAI. Therefore, HAI is effective only in tumors limited to the liver.

CLINICAL EXPERIENCE WITH HAI

Early studies with HAI

Early studies with HAI were conducted using fluoropyrimidines, 5-fluorouracil or floxuridine. Early experience with HAI of 5-fluorouracil in different primary tumors was summarized by Ansfield et al.³⁶. Of 428 patients included in the cohort, 381 had colorectal primary. The definition of response in this early study differed from the current definitions relying on imaging, and the response was defined as reduction of liver size, decrease in liver enzymes or, in case of hyperbilirubinemia, serum bilirubin. The response was not analyzed according the tumor type, but in the whole cohort the response defined by the criteria outlined above was observed in 55% of patients. It has been noted that in 36 jaundiced patients with colorectal primary the jaundice disappeared in 11 cases.

In 1980s and early 1990s several randomized trials comparing HAI of fluoropyrimidines with systemic administration of fluoropyrimidines or best supportive care³⁷⁻⁴². In these studies, usually HAI resulted in higher objective response rate. It has also been demonstrated that HAI results in superior quality of life compared with systemic chemotherapy¹⁸. However, the survival advantage was evident only in some of these trials that had also untreated patients in the control arm. All these studies were underpowered to detect a survival advantage. Moreover, the intent-to-treat analyses in these trials included substantial number of patients in the HAI arm who could not be treated because of technical problems, and sometimes a cross-over from the control to the HAI was allowed. Only one study failed to demonstrate higher response rate for HAI, probably because of methodological issues that prevented the administration of HAI in 37% of randomized patients and in another 29% of patients being administered less than 6 cycles of therapy⁴³. A survival advantage was demonstrated in a more recent randomized trial comparing a systemic bolus regimen of 5-fluorouracil and leucovorin with the combination of HAI of floxuridine and dexamethasone¹⁹. In this trial, both objective response rate (47% vs. 24%) and overall survival (median 24 vs. 20 months) was significantly better in the HAI arm. However, these results were published at a time when the systemic chemotherapy evolved several steps from the control arm in this study. Nevertheless, this trial constitutes proof of the principle of the superiority of HAI over systemic administration of cytotoxic agents. The results of these randomized trials were summarized in a few meta-analyses^{17,44,45}. In the most recent meta-analysis, 10 randomized clinical trials that enrolled a total of 1277 patients were analyzed⁴⁵. This meta-analysis confirmed significantly higher response rate for HAI (43% vs. 18%), but the difference in overall survival (median 16 vs. 12 months) was not statistically significant.

In most of the trials, floxuridine, the drug with better pharmacokinetic parameters of regional selectivity, was used for HAI. On the other hand, 5-fluorouracil is more commonly available and has been widely used in clinical practice. However, in one study comparing HAI of floxuridine, HAI of 5-fluorouracil/leucovorin and systemic administration of 5-fluorouracil/leucovorin the clinical efficacy in both HAI was comparable (response rate 43% and 45%, respectively) (ref.⁴⁶), suggesting that the pharmacokinetic advantage of floxuridine may not translate into superior clinical efficacy. Fluoropyrimidines used in the early studies of HAI, 5-fluorouracil and floxuridine, still constitute the backbone of most HAI regimens used for colorectal cancer liver metastases. With the advent of combination chemotherapy, HAI regimens administering fluoropyrimidine in monotherapy are no longer used as first-line treatment. However, as indicated by a recent report the HAI of floxuridine may represent an effective second or third line treatment option⁴⁷. The most important randomized trials comparing HAI with systemic chemotherapy are summarized in Table 1.

Efficacy of HAI utilizing agents other than fluoropyrimidines

The current standard of systemic chemotherapy in patients with metastatic colorectal carcinoma is the administration of fluoropyrimidines with irinotecan, oxaliplatin or both agents, based on demonstration of improved outcome in randomized clinical trials^{3,4,48,49}. The improvement of survival associated with the advent of new cytotoxic agents was even noted in some retrospective cohorts of patients treated with HAI and, subsequently, with systemic chemotherapy⁵⁰. As the combination chemotherapy replaced fluoropyrimidine monotherapy or administration of fluoropyrimidines potentiated by leucovorin as standard of care for the systemic treatment of metastatic colorectal carcinoma, the potential of HAI of oxaliplatin and irinotecan was also investigated. In most of these studies, oxaliplatin, irinotecan or other agents were combined with fluoropyrimidines. "Hybrid" chemotherapy regimens combining HAI of fluoropyrimidines and systemic administration of a second cytotoxic agent, or vice versa, were also studied.

Oxaliplatin and irinotecan became widely available in the late 1990s. In an earlier era, only drugs with marginal single-agent activity in metastatic colorectal carcinoma could be combined with HAI of fluoropyrimidines. While mitomycin C alone⁵¹, or in combination with 5-fluorouracil and anthracyclines⁵² has demonstrated activity when administered as HAI, other retrospective data indicate that addition of mitomycin C or anthracyclines to the combination of 5-fluorouracil and leucovorin has little effect on survival⁵⁰. In another study Kemeny et al.⁵³ randomized 95 patients to the HAI of floxuridine monotherapy or the HAI of the combination of mitomycin C and carmustine. The trend to higher response rate and longer overall survival did not reach statistical significance.

Encouraging activity has been reported for the HAI of oxaliplatin in a number of studies⁵⁴⁻⁶⁰. In a phase I study

Table 1. The most important randomized trials comparing HAI with systemic chemotherapy in patients with colorectal cancer liver metastases.

Reference	Institution or organization	HAI arm	IV arm	Patients enrolled HAI./IV	Randomized/evaluated (in the HAI arm)	RR (%) HAI/IV (p)	Parameter of survival evaluated	Survival HAI/IV (p)	Notice
(ref. ¹⁹)	Cancer and Leukemia Group B	FUDR	5FU+FA	68/67	68/59	47/24 (0.01)	median (months)	24.4/20 (0.003)	
(ref. ³⁷)	Cancer Research Campaign	FUDR	BSC or systemic CT	51/49	-	12* /30* (0.01)	median (days)	405/226 (0.03)	BSC possible in the control arm
(ref. ³⁸)	National Cancer Institute	FUDR	FUDR	32/32	32/21	62/17 (0.03)	2-year survival (%)	22 /15 (NS)	significantly improved survival in patients with negative hepatic lymph nodes
(ref. ³⁹)	Northern California Oncology Group	FUDR	FUDR	67/76	67/50	42/10 (0.0001)	median (days)	503/484 (NS)	crossover to HAI in 28 patients
(ref. ⁴⁰)	Memorial Sloan-Kettering Cancer Center	FUDR	FUDR	48/51	-	50/20 (0.001)	median (months)	17 /12 (NS)	cross-over in 60%
(ref. ⁴¹)	Mayo Clinic	FUDR	5FU	33/36	33/31	48/21 (0.02)	median (months)	12.6 /10.5 (NS)	extrahepatic spread in 19% of patients
(ref. ⁴²)	Groupe d'Etudes et de Recherches des Tumeurs Hépatique	FUDR	5FU or BSC	82/84	82/70	43/9 (0.05)	1-year survival (%)	64/44 (0.02)	BSC was possible in the control arm
(ref. ⁴³)	Medical Research Council	5FU+/FA	5FU+FA	145/145	145/95	22/19 (NS)	2-year survival (%)	23/13 (0.02)	
(ref. ⁴⁶)	German Cooperative Group on Liver Metastases	FUDR	5FU+FA	54 /57	54/37	43/20 (0.020)	median (months)	14.7/14.8 (NS)	of patients randomized to HAI 37% untreated; 29% received less than 6 cycles
		5FU+FA		57	57/40	45 (0.01)		18.7 (NS)	

*percentage of liver involvement; 5FU 5-fluorouracil; BSC best supportive care; CT chemotherapy; FA folinic acid (leucovorin); FUDR fluorouridine; HAI hepatic arterial infusion; IV intravenous; NS not significant; RR response rate

of oxaliplatin monotherapy administered as 30-minutes HAI in pre-treated patients, the dose limiting toxicity was reached at 175 mg/m² (ref.⁶⁰). The dose recommended for further study was 150 mg/m², and using this dose, objective response rate of 33% and a disease control rate of 50% were obtained. Median survival was 13 months⁶⁰. When administered as continuous 5-day HAI at a dose of 20 mg/m²/day the objective response rate with oxaliplatin monotherapy was 46% and disease control rate was 67%, with median survival being 19 months⁵⁸. However, similarly to systemic chemotherapy most studies of HAI of oxaliplatin reported on the combinations with 5-fluorouracil and leucovorin. In a phase I study the recommended dose of oxaliplatin administered as HAI in combination with 5-fluorouracil and leucovorin was 125 mg/m² every 3 weeks⁵⁴. A very promising response rate of 56% was reported in this phase I trial⁵⁴. HAI of oxaliplatin was also administered in a bimonthly regimen at a dose of 100 mg/m² in combination with 5-fluorouracil and leucovorin administered as HAI (ref.^{55,56}) or systemically^{57,59}. When administered as second or higher line of therapy, the objective response rate and overall survival ranged between 24% to 55% and 16 to 18 months, respectively⁵⁵⁻⁵⁷. In a predominantly first-line population, the response rate of HAI of oxaliplatin combined with systemic administration of 5-fluorouracil and leucovorin was 64% and median survival was 27 months⁵⁹. Abdominal pain has been reported as a peculiar side effect of HAI of oxaliplatin in a number of studies⁵⁸⁻⁶⁰. The results of HAI of the combination of oxaliplatin, 5-fluorouracil, leucovorin and mitomycin C have also been reported in a small pilot study with promising activity⁶¹. Systemic oxaliplatin was also combined with HAI of 5-fluorouracil resulting in a response rate of 41% (ref.⁶²). In a retrospective report, the experience with sequential administration of HAI of 5-fluorouracil followed by the systemic combination of oxaliplatin, 5-fluorouracil and leucovorin (FOLFOX) was described with response rates after HAI and FOLFOX of 85% and 35%, respectively⁶³.

A number of reports have also been published on HAI of irinotecan⁶⁴⁻⁶⁶. In a phase I trial maximum tolerated dose of irinotecan administered for 5 days every 3 weeks was 25 mg/m² (ref.⁶⁷). The conversion rate to SN-38, the active metabolite of irinotecan, was higher with HAI when the pharmacokinetic data were compared with intravenous infusion in the same individual. The systemic concentrations of irinotecan were lower with HAI while systemic concentrations of SN-38 were similar for HAI and intravenous infusion⁶⁷. The liver tissue is characterized by high activity of carboxylesterase that converts irinotecan to SN-38 (ref.⁶⁸), and this enzymatic activity may be responsible for the higher conversion rate to SN-38 with HAI. From another phase I trial examining a different schedule, the recommended dose of irinotecan administered as HAI monotherapy emerged at 200 mg/m² every 3 weeks⁶⁴. The response rate in the phase I cohort was 14% while in the phase II cohort of previously treated patients the response rate was 33%. In a pilot experience in 15 patients, objective response was observed in 5 and

stable disease in 7 patients⁶⁵. In a phase II trial HAI of irinotecan, 5-fluorouracil and leucovorin was combined with oral administration of UFT (combination of tegafur and uracil in 1 : 4 molar ratio) and leucovorin in 31 patients with metastatic colorectal carcinoma⁶⁶. Partial response was observed in 20 (65%) patients, and median survival was 36 months. Irinotecan can also be administered using sulfonate hydrogel microsphere, drug-eluting bead, irinotecan (DEBIRI). In a study that enrolled 55 heavily pretreated metastatic colorectal carcinoma patients objective response was observed in 36 (65%) patients, median progression-free survival was 11 months and median survival was 19 months⁶⁹. In a phase I/II study, systemic administration of irinotecan was combined with HAI of 5-fluorouracil and oral UFT (ref.⁷⁰). The recommended dose of irinotecan from the phase I part of the trial was 140 mg/m². Of 22 patients enrolled in the phase II part of the study, 19 patients (86%) had partial response and 14 patients subsequently underwent liver resection⁷⁰. Systemic administration of irinotecan was also studied in combination with HAI of floxuridine in 39 heavily pretreated patients resulting in 44% response rate with median survival of 20 months⁷¹.

HAI of the combination of oxaliplatin, irinotecan and 5-fluorouracil administered in a chronomodulated regimen was studied in 29 heavily pretreated metastatic colorectal carcinoma patients⁷². Partial response was observed in 10 patients (35%) and resection could be performed in 4 patients. Median progression-free survival and overall survival were 5 months and 18 months, respectively⁷². Chen et al. reported on HAI of oxaliplatin, irinotecan and doxifluridine in combination with systemic administration of doxifluridine and leucovorin in 32 patients⁷³. Objective response was noted in 61% of patients treated in the first line and 29% of pretreated patients.

The number of cytotoxic agents active in metastatic colorectal carcinoma is limited. Thus, it is not surprising that few studies are available on the activity of agents other than fluoropyrimidines, oxaliplatin or irinotecan administered as HAI. In fact, most other agents were combined with one of the drugs with established activity in metastatic colorectal carcinoma. In a pilot study, HAI of the combination of oxaliplatin and raltitrexed was studied in 17 patients pretreated by both oxaliplatin and irinotecan⁷⁴. Three complete responses and 8 partial responses were observed for an overall response rate of 65%. The median survival of 28 months in this heavily pretreated cohort is encouraging, but, similar to the experience with systemic administration of raltitrexed, serious toxicity was found, and one patient with grade 4 neutropenia died of septic shock. HAI of high-dose melphalan (200 mg) was studied in 30, mostly pre-treated patients administered HAI regimen using isolated hepatic perfusion⁷⁵. Partial response was observed in 15 patients, but the treatment was complicated by significant hepatic toxicity, including one death from liver failure. In a phase II trial, HAI of pirarubicin in combination with systemic 5-fluorouracil and leucovorin resulted in a response rate of 32% (ref.⁷⁶). Objective response was also reported in 4 out of 17 (24%)

of patients treated with HAI of fotemustine⁷⁷. Anecdotally, a long-term complete response has been reported after HAI of the combination of oxaliplatin and gemcitabine⁷⁸.

HAI combined with targeted therapy

The advent of targeted therapy has had major impact on the management of metastatic colorectal carcinoma^{5,79,80}. It has been demonstrated in prospective randomized trials that the administration of targeted agents results in improved outcomes, including significant prolongation of overall survival, in both chemotherapy-naïve and pre-treated patients with metastatic colorectal cancer. Currently, three targeted agents are registered for the therapy, antibody against VEGF bevacizumab⁸¹ and antibodies against EGFR cetuximab^{6,82} and panitumumab⁸⁰. Most promising results were found when these monoclonal antibodies were combined with cytotoxic agents^{5,81,82}.

So far, only a limited number of reports of pilot studies that investigated combinations of HAI of cytotoxic agents with anti-VEGF or anti-EGFR monoclonal antibodies have been published^{83–86}. Neyns et al.⁸³ reported pilot experience with systemic administration of cetuximab combined either with HAI of oxaliplatin or systemic irinotecan and HAI of 5-fluorouracil and leucovorin in 8 patients with liver metastases of colorectal carcinoma. Partial response was observed in 5 patients. An unusual side effect of cystic bile duct dilatation was noted in 2 patients. The combination of HAI of oxaliplatin with systemic administration of 5-fluorouracil, leucovorin and bevacizumab was studied in 6 patients with malignancies refractory to standard treatment (including 3 patients with colorectal carcinoma liver metastases) (ref.⁸⁴). Among patients responding to this therapy was one patient with colorectal primary. The combination of HAI of oxaliplatin with systemic administration of 5-fluorouracil, leucovorin and bevacizumab was further investigated in a phase I trial in 57 heavily pretreated primary and secondary liver tumors⁸⁶. The maximum tolerated dose of oxaliplatin was 140 mg/m². Among 28 patients with colorectal primary, 3 patients (11%) had partial response and 11 patients (32%) had stable disease for more than 4 months. The effect of addition of bevacizumab to HAI of floxuridine was also investigated in a phase II randomized trial in patients after liver resection⁸⁵, but no apparent benefit of the combined therapy was evident.

Theoretically, the combination of HAI of oxaliplatin with bevacizumab may be of advantage because of the protective effect of bevacizumab on oxaliplatin-induced liver injury⁸⁷. On the other hand, the biliary toxicity of floxuridine in combination with bevacizumab was increased⁸⁵. The efficacy of HAI in combination with cetuximab or bevacizumab seem to be promising, especially in heavily pretreated patients. The combinations of HAI with targeted agents should be explored in further prospective trials.

Advantages and pitfalls of HAI

In selected patients, HAI is a highly effective therapeutic method. However, a number of factors limit the effectiveness or use of this treatment approach, includ-

ing catheter or port system-related complications, the presence of extrahepatic metastases, and increased risk of hepatic toxicity. As summarized above, HAI has the advantage of higher efficacy and, importantly, lower systemic toxicity. Decreased systemic exposure may be viewed as an advantage as well as a drawback since it is associated with decreased toxicity, but also with suboptimal systemic exposure with less activity on extrahepatic disease⁸⁸. These advantages and disadvantages should be weighted when deciding about indication for HAI.

For HAI, an intraarterial catheter needs to be introduced into the hepatic artery. Technical problems with the catheter, port system or implanted pump are common and frequently result in the delay or discontinuation of therapy^{62,89}. These technical problems also manifested in clinical trials, and, in some studies, a substantial proportion of patients randomized to HAI could not be treated⁴³. Historically, the placement of the intraarterial catheter with subcutaneous chamber of the port system or pump was performed surgically, but currently intraarterial catheters with the port system are commonly introduced by interventional radiologists^{90,91}. Retrospective analysis comparing the surgical versus interventional route of implantation suggest that the rate of complications tend to be higher and the duration of port system function is significantly shorter when the surgical approach is used⁹¹. In fact, in many centers, implantation of the catheter by interventional radiology is currently preferred over the surgical approach⁸⁹.

An important cause of failure of HAI is the manifestation of extrahepatic metastases. When cytotoxic agents are administered solely using HAI, the systemic drug concentrations are lower, resulting in the emergence of extrahepatic metastases that could be potentially resistant to cytotoxic agents that were administered via HAI. To counter this problem, HAI has been combined with systemic administration of anticancer agents. An issue of obvious importance is the selection of patients with isolated hepatic metastases (liver-only disease) for HAI.

Theoretically, it could be thought that the hepatotoxicity of cytotoxic agents administered by HAI might present a serious problem, but in clinical practice the liver toxicity of agents administered in HAI regimens is, with few exceptions, limited. Hepatic toxicity of chemotherapy, whether administered as HAI or systemically, is a significant issue in patients with hepatocellular carcinoma because of the presence of liver cirrhosis in the majority of patients, but cirrhosis is rare in the population of patients with colorectal carcinoma liver metastases and, consequently, the incidence of serious hepatic toxicity is low. Although from the pharmacokinetic perspective HAI of floxuridine has the biggest advantage, the HAI of this agent is associated with significant biliary toxicity, and floxuridine has to be administered with dexamethasone. HAI of floxuridine with or without dexamethasone was studied in a small randomized trial⁵³. The addition of dexamethasone not only resulted in less biliary toxicity, but also in a higher response rate (71% vs. 40%). Dexamethasone itself may have some antitumor activity, possibly mediated through

inhibition of angiogenesis⁹². Oxaliplatin, whether administered as HAI or systemically, also induces a peculiar form of liver toxicity manifesting as sinusoid obstruction syndrome^{93,94}. Liver toxicities associated with the administration of agents commonly used in colorectal carcinoma include non-alcoholic fatty liver disease after 5-fluorouracil and steatohepatitis after irinotecan⁹⁵. These toxicities may complicate liver surgery when neoadjuvant strategy is employed⁹⁵, but it is currently not known whether these toxic side effects are more prominent with HAI. So far, no warning safety signals regarding hepatic toxicity have been reported from trials using HAI of oxaliplatin or irinotecan.

The problems associated with the use of HAI had an obvious effect on clinical trials that studied this approach. In general, these studies have some common problems, including low statistical power due to the need to select patients with isolated liver metastases and inability to administer HAI in a significant proportion of the intention-to-treat population due to catheter-related problems. On the other hand, lower systemic toxicity is the major advantage of HAI in this patient population. Systemic administration of anticancer therapy in patients with metastatic colorectal carcinoma is frequently accompanied by side effects, with hematological and gastrointestinal toxicities⁹⁶ being the most frequent complications. A more favorable safety profile of HAI has been apparent across the clinical trials. Importantly, it has been demonstrated that lower toxicity translates into superior quality of life in patients treated with HAI (ref.¹⁸). Also toxicities associated with targeted treatments, e.g. skin toxicity associated with the anti-EGFR therapy⁹⁷, have major impact on the quality of life.

The identification of clinical and laboratory parameters that could predict response is of major importance in medical oncology. This issue is even more important for an invasive approach like HAI. An obvious clinical predictive factor is the absence of extrahepatic metastases. Recently, much attention in the management of colorectal carcinoma has been focused on laboratory predictive and prognostic factors, i.e. biomarkers. Only limited information is available on the biomarkers that could predict the response to HAI (ref.¹⁹). In one trial, the combination of the tumor expression of thymidylate synthase and p53 was predicting overall survival¹⁹. In clinical practice, the same biomarkers are utilized in patients treated with HAI as in the metastatic colorectal cancer patients in general. In patients with primary and secondary liver tumors, including patients with liver metastases of colorectal carcinoma an immune deficit that manifests as low number of CD4⁺ T-cells is frequently present⁹⁸. An inverse correlation has been described between peripheral blood CD4⁺ T-cells and urinary concentrations of neopterin, a biomarker of systemic immune response⁹⁸. High neopterin concentrations are an independent predictor of poor prognosis in patients with metastatic colorectal carcinoma⁹⁹.

HAI and other liver-directed procedures

As mentioned above, the liver is the most common site of distant metastases. Different liver-directed therapies

have been proposed for the treatment of primary or secondary (metastatic) liver tumors. Liver-directed therapies may be distinguished into direct methods that include resection, intratumoral injection or radiofrequency ablation (RFA) and vascular methods that include HAI. With regard to liver-directed therapies, tumors metastasizing to the liver may be distinguished into 3 categories based on how frequently are liver-directed treatments appropriate in individual patients; often appropriate, occasionally appropriate or seldom appropriate¹⁰⁰. Because of the biology and pattern of metastatic spread, colorectal carcinoma is an example of tumor that is often appropriate for liver-directed therapies. In fact, given the high incidence of this tumor, colorectal carcinoma is in many countries the most common indication for liver-directed therapies, including liver resection or HAI.

Although, with few exceptions, metastatic solid tumors are regarded as incurable disease, a small proportion of patients with colorectal carcinoma liver metastases can be cured with liver resection. Resection is feasible only in a minority of patients, and long-term cure is achieved in only 30-40% of patients who undergo the procedure¹⁰¹. However, there is cumulative evidence that multimodality approach that includes both liver resection and chemotherapy may result in more patients being able to undergo resection as well as in improved long-term survival after resection. Because of high efficacy of HAI in patients with isolated liver metastases, the potential of this approach in neoadjuvant and adjuvant setting has been studied.

As outlined above, patients with isolated liver metastases in whom primary liver resection can be performed represent only a minor proportion of the population of patients with metastatic colorectal cancer. Thus, prospective trials of adjuvant therapy in patients undergoing liver resection were difficult in terms of recruiting sufficient patients to answer the questions regarding the efficacy of this treatment. It is therefore not surprising that definitive evidence for the role of adjuvant chemotherapy, systemic or HAI, in patients after liver resection is still lacking. Kemeny et al. randomized 156 patients after liver resection to systemic 5-fluorouracil/leucovorin or the same systemic therapy combined with HAI of floxuridine and demonstrated prolongation of survival in the combined therapy arm (median 72 vs. 59 months) (ref.¹⁰²). In a subsequent trial, Kemeny et al. compared the observation (no treatment) with the combination of HAI of floxuridine and continuous infusion of 5-fluorouracil¹⁰³. Significantly more patients were free of liver recurrence (46% vs. 25%) or any recurrence (67% vs. 43%) in the combined therapy arm, but because of limited sample size, prolongation of survival could not be demonstrated. In another trial comparing HAI of 5-fluorouracil and leucovorin versus observation in patients after liver resection there was no evidence of improved survival with the use of HAI, but, like many trials in patients with unresectable metastases, a significant proportion of patients randomized to HAI were never treated¹⁰⁴. Adjuvant administration of HAI after liver resection has also been explored in combination with systemic administration of other drugs or in regimen alternating HAI with systemic chemotherapy. In a pilot

study Kemeny et al. combined HAI of floxuridine and dexamethasone with systemic administration of irinotecan¹⁰⁵. The maximum tolerated dose of irinotecan was 200 mg/m². Two-year survival was 89%, but extrahepatic recurrence was evident in most patients. A trend of improved outcome was noted in patients treated with maximum tolerated dose. In a phase II trial, HAI of floxuridine and dexamethasone was alternated with systemic administration of oxaliplatin and capecitabine¹⁰⁶. The 2-year survival rate was 88%, and median disease-free survival was 33 months. Although these results of combined HAI and systemic multidrug therapy are promising, they remain to be confirmed in prospective randomized trials. The results of randomized trials studying adjuvant systemic chemotherapy or HAI after liver resection were also studied in meta-analyses^{107,108}. In a meta-analysis focusing on HAI, the trend of improved survival did not reach statistical significance¹⁰⁷. In a more recent meta-analysis studying both systemic chemotherapy and HAI both methods improved recurrence-free survival, but there was no significant survival difference¹⁰⁸.

Neoadjuvant chemotherapy represents another approach aimed at increasing the cure rate of patients with colorectal cancer liver metastases. Different regimens of systemic chemotherapy or HAI have been evaluated in the neoadjuvant setting in this patient population¹⁰⁹. The assessment of the potential of neoadjuvant approach in improvement of long-term results of liver resection was even more difficult than in the adjuvant setting. For obvious reason, the treating physicians were reluctant to enroll patients with clearly resectable lesions into trials of therapies that could potentially fail, resulting in non-resectability in a case deemed originally resectable. The studies of neoadjuvant chemotherapy in colorectal cancer liver metastases have therefore focused more or less on selected patients with metastases that were originally judged unresectable, or the resectability was considered questionable. Most studies on the effect of HAI on resectability and long-term survival are retrospective series. In one of the earlier studies, promising neoadjuvant activity has been reported by Link et al. for a combined HAI regimen⁵². Goéré et al. reported on a series of 87, mostly pre-treated patients treated with the combination of HAI of oxaliplatin with systemic 5-fluorouracil and leucovorin⁸⁹. In this series, resection or RFA was performed in 21 patients, and 5-year survival after surgery was 56%. The resection rate was higher in patients who received HAI in the first line. In another analysis of 49 patients treated with HAI of floxuridine with systemic oxaliplatin and irinotecan, objective response was observed in 45 patients (92%) and the resection was performed in 23 patients (47%) (ref.¹¹⁰). Again, the response and resection rates were higher in patients treated in the first line. Liver resections were also reported after HAI administered as second or third line of therapy of colorectal carcinoma liver metastases^{47,57,71,72}. HAI has also been successfully combined with RFA (ref.^{89,111}). In a prospective study, HAI of floxuridine was combined with RFA or RFA plus resection in 21 patients with up to 10 lesions¹¹¹. The median liver-specific disease-free survival and overall survival were 17 and 30 months, respectively.

Adjuvant regional chemotherapy in patients without manifest liver metastases

Adjuvant therapy may be defined as the treatment of distant metastases that are not detectable by conventional imaging studies, but are presumed to be present based on expected recurrence rates. Given the high rate of metachronous liver metastases in patients with colorectal cancer, it is not surprising that regional approaches have been also investigated in the adjuvant setting in patients with stage II or III colorectal carcinoma. As outlined above, small subclinical metastases, unlike overt metastases diagnosed with routine imaging, are supplied by both hepatic artery and portal vein system. Thus both HAI and portal vein infusion (PVI) have been studied in the adjuvant setting in a number of studies.

HAI has also been combined with other regional approaches. Xu et al. reported a trial that randomized 222 patients with stage II and III colorectal carcinoma to preoperative oxaliplatin and floxuridine administered as HAI and into the artery supplying the primary tumor¹¹². The preoperative regional chemotherapy resulted in significant reduction of the risk of liver metastasis, any recurrence and death in patients with stage III disease, while the trend of improved outcome in patients with stage II tumors did not reach statistical significance. The results of randomized trials of HAI or PVI have recently been summarized in a recent meta-analysis¹¹³. This meta-analysis included 2 trials of HAI and 7 trials of PVI. Perioperative administration of HAI was associated with significant improvement of 5-year mortality rate (13% vs. 27%; HR 0.46; $P=0.0002$) over surgery alone, but the no effect on mortality rate was evident for PVI. Administration of HAI also resulted in significantly lower rate of liver metastases (11% vs. 25%; $P=0.0002$) (ref.¹¹³).

Current role of HAI in the management of patients with colorectal cancer liver metastases

HAI may be regarded as an investigational method that has been studied extensively in clinical trials. Despite studies that have been performed with HAI over the last five decades, the role of HAI in the management of patients with hepatic metastases of colorectal cancer remains controversial. Recently, Kemeny defined 3 circumstances under which HAI could be considered in clinical practice, including HAI as adjuvant treatment in patients after liver resection, HAI as a second or higher line of therapy in patients failing standard front line regimens, or HAI as neoadjuvant therapy to convert to resectability¹¹⁴. All these indications are supported by extensive data, although all studies supporting this use suffered from similar problems to other trials of HAI. "Hybrid" chemotherapy regimens that combine HAI and systemic administration of cytotoxic agents could be of advantage in this setting because of the potential to control hepatic as well as extrahepatic disease, but this has so far not been proven in randomized clinical trials. One distinct advantage of HAI in the neoadjuvant or adjuvant therapy in association with liver resection is less limitation regarding the timing of the treatment before and after surgery. Bevacizumab, the targeted agents most commonly administered in combination with che-

motherapy in the first-line setting, impairs wound healing and an interval of at least 28 days is recommended between the administration of bevacizumab and surgery. Moreover, administration of bevacizumab is considered risky or even contraindicated in patients with some comorbidities, e.g. thromboembolic disease or inflammatory bowel disease, and HAI of combined chemotherapy may provide an effective alternative to the systemic administration of bevacizumab with combination chemotherapy.

The efficacy of HAI administered as second or higher line of therapy varies significantly. Relatively low efficacy has been reported in studies using fluoropyrimidine monotherapy¹¹⁵, but high response rate and prolonged survival have been reported in patients treated with combined regimens^{55-57,72}. Obviously, the patient selection plays a significant role in the second or higher line therapy setting, and prolonged survival has been documented in individual patients, even when using HAI of drugs administered earlier in the course of therapy⁷².

Even at the time when HAI offered the highest disease control rates of all available therapies, the utilization of this approach differed markedly among institutions. With the introduction of targeted therapies, the use of HAI has decreased even in centers that have been the most ardent advocates of this method. However, there are certainly patients who may benefit from this approach, and HAI should remain an option in the therapeutic armamentarium for patients with isolated liver metastases of colorectal carcinoma.

CONCLUSIONS

In spite of all its limitations, HAI remains a promising approach in the therapy of colorectal cancer patients with isolated liver metastases. The data on HAI of fluoropyrimidines are currently more or less only of historical interest, since the standard of care has changed. Promising activity was observed with HAI of combination chemotherapy. The concurrent systemic administration of cytotoxic agents could limit extrahepatic disease as the cause of failure. Combined regimens comprising HAI of cytotoxic drugs and systemic administration of cytotoxic agents have demonstrated promising results and should be further investigated. Moreover, there is cumulative body of evidence that the combined HAI regimens increase resection rates and as part of multidisciplinary treatment approach may cure selected patients. Current standards of care for metastatic colorectal carcinoma comprise the combination of monoclonal antibodies targeting VEGF or EGFR in combination with chemotherapy, but, currently, only limited data are available on the combination of HAI with targeted agents. Future studies should specifically concentrate on identifying a regimen that would result in increased cure rates in patients with isolated hepatic metastases. Thus, exploiting anatomical selectivity may still be a useful approach even in the era of targeted agents.

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CONFLICT OF INTEREST STATEMENT

Author's conflict of interest disclosure: The author stated that there are no conflicts of interest regarding the publication of this article.

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