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Review

Hepatic Metastases of Colorectal Cancer: Locoregional Intra-arterial Treatment

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Abstract. *A radical resection alone of colorectal hepatic metastases is possible in only 10-20% of the patients but, when resection and ablation are combined, the rate of radicalism can improve. A regional hepatic intra-arterial chemotherapy infusion (HAI) has been introduced in the clinical practice, as a possible alternative approach to systemic chemotherapy. Nevertheless, the introduction of new systemic therapies with monoclonal antibodies, combined to irinotecan or oxaliplatin, recently improved response rates and overall survival in these patients. Aiming to evaluate a possible influence of HAI in these new treatments, the most important studies underlining the evolution of intrahepatic administration in recent years are reviewed.*

Hepatic metastases are the major cause of morbidity and mortality in patients with gastrointestinal carcinomas (1). At present, resection is the most important therapeutic option and sometimes can be performed simultaneously with the surgical treatment of the primary tumour. The location, vessel proximity, number and size of the lesions, together with the presence of concomitant disease, provide the basis for the decision to perform a resection and influence survival.

A curative resection of colorectal hepatic metastases is possible in only 10-20% of patients. In these cases, 25-51% of them are still alive after 5 years, according to several prognostic factors. The median survival time (MST) is roughly 30 months and disease free survival (DFS) at 5 years is 34%. Longer survival is observed in cases with fewer than 4 lesions, lesions smaller than 4 cm, absence of extrahepatic disease, presence of lesions appearing more than 2 years after the resection of a stage I or II colorectal cancer and normal CEA level (2). When hepatic resection is possible, no subsequent standard therapeutic approach is yet defined.

When radical surgery resection of liver metastases is not possible (80-90% of cases), chemotherapy must be considered as a pure palliative and/or as a possible neo-adjuvant approach. In this case, the MST is about 24 months (3). Regional hepatic intra-arterial chemotherapy infusion (HAI) has been introduced in the clinical practice, as a possible alternative approach to systemic chemotherapy. Microwave, radiofrequency (RF), ultrasound ablation, laser induced interstitial therapy (LITT), cryotherapy, local drug administration, such as alcohol injection, endotumoral chemotherapy or immunotherapy (tumour antibodies, which carry a local active agent), regional chemo-embolisation and intra-arterial radiation therapy are other local ablative alternative techniques. All ablative techniques can be performed with low mortality and morbidity rates but, to date, small advantages in terms of survival have been reported.

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Intra-arterial Chemotherapy

The first passage through the liver can increase the intrahepatic chemotherapeutic agent level, limiting systemic toxicity. Hepatic metastases and, probably residual tumour after hepatic resection, receive blood supply from the hepatic artery, while normal liver cells receive their blood from the portal vein. HAI exposes metastases to high drug concentrations, sparing normal liver tissue and controlling in this way, hepatic disease progression.

Floxuridine (FUDR)

a) Neo-adjuvant therapy: From the 1980s to the 1990s, the first phase III randomised studies on HAI in non-resectable liver-only metastases reported a response rate (RR) of 42-62% *versus* 10-21%, obtained after systemic chemotherapy

Table I. *Neo-adjuvant randomised trials of FUDR HAI (I arm) versus systemic chemotherapy (II arm).*

Authors	II Arm	No. of patients	RR (%)	MST (months)
Kemeny *et al.* (4)	FUDR *i.v.*	48 *vs.* 51	50 *vs.* 20 $p=0.001$	17 *vs.* 12 (n.s.)
Chang *et al.* (5)	FUDR *i.v.*	32 *vs.* 32	62 *vs.* 17 $p<0.003$	17 *vs.* 11 (n.s.)
Hohn *et al.* (6)	FUDR *i.v.*	67 *vs.* 76	42 *vs.* 10 $p=0.0001$	17 *vs.* 16 (n.s.)

n.s.=not significant; *i.v.*=intravenous; FUDR=fluorodeoxyuridine; HAI=intra-arterial; RR=response rate; MST=median survival time.

Table II. *Neo-adjuvant FUDR HAI infusion (phase II trials).*

Years	Drugs (ref.)	RR (%)	MST (months)
1980-1990	FUDR HAI *vs.* FUDR *i.v.* (4-7)	42-62 *vs.* 10-21	12.6 *vs.* 17 (n.s.)
1990-2000	FUDR HAI *vs.* 5FU bolus (8)	48 *vs.* 21	12.6 *vs.* 10.5 (n.s.)
	FUDR HAI *vs.* 5FU HAI *vs.* 5FU bolus (9)	45 *vs.* 43 *vs.* 20	12.7 *vs.* 18.7 *vs.* 17.6 (n.s.)
	FUDR HAI + desametasone + LV (14)	56-78	23-24.8
	FUDR HAI → 5FU/LV bolus (15, 16)	53	10

n.s.=not significant; *i.v.*=intravenous; FUDR=fluorodeoxyuridine; HAI=intra-arterial; 5FU=5-fluorouracil; LV=leucovorin; RR=response rate; MST=median survival time.

alone (4-8) (Tables I, II). Most of these studies involved 14 days-FUDR HAI infusion per month, *via* a totally implantable constant-infusion device. An increased RR did not translate into a significant increased overall survival (OS), when HAI was compared with systemic chemotherapy. MST ranged from 12.6 to 17 months and 56% of patients receiving HAI developed subsequent extrahepatic disease (4). When analysed, part of those studies, which mandated a cross-over of patients, who had failed to respond to intravenous (*i.v.*) treatment to the HAI chemotherapy arm, all the advantages of the HAI arm in terms of survival were obscured (5, 6). Moreover, the majority of these trials were too small and under-powered to assess significant survival differences, between treatment arms (4, 8). Nevertheless, in the only large randomised trial (9) on 168 unresectable patients, in which 3 different types of approach were studied (5-Fluorouracil (5FU) HAI *versus i.v.* 5FU bolus *versus* FUDR HAI), similar data were confirmed. In the study, patients were randomised before surgery so that the two groups of patients assigned to the HAI arms had more extensive staging, including laparotomy. The HAI FUDR therapy was relatively standard. The 5-day 5FU/leucovorin (LV) regimens were initially the same in dose and schedule, whether they were given intrahepatically or systemically; after they required dose reduction. Eighteen patients assigned to the HAI arms were found to have extrahepatic disease, and many of them were given the systemic chemotherapy treatment. Overall, 86 patients received some form of cross-over therapy, with most patients on the systemic arm not receiving such treatment. Mortality was considerably higher in the group who underwent surgical exploration, thereby, further decreasing the likelihood of detecting a survival advantage in the group assigned to the hepatic infusion arms. The median time to progression (TTP) was respectively 9.2, 6.6, and 5.9 months (n.s.), in contrast with previous results obtained with FUDR. The median RR after intrahepatic treatment was 43% to 45% (20% for systemic 5FU/LV), but extrahepatic progression was 13% after 5FU/LV and 41% after FUDR. The high rate (40%) of side-effects (stomatitis, nausea and vomiting, skin irritation, diarrhoea) after intrahepatic 5FU/LV indicated that its cytotoxic levels were achieved in the systemic circulation (the toxicity profile of 5FU/LV was similar, whether the drugs were given intrahepatically or systemically). The good RR after 5FU/LV HAI did not concur with a significant increase in TTP or OS (probably for the high mortality rate in this group) (12.7 months for the FUDR HAI to 18.7 months for 5FU/LV HAI and 17.6 months for systemic 5FU/LV, respectively); furthermore, the high toxicity and the MST similar to those obtained with FUDR HAI, made 5FU/LV HAI inadvisable, as a therapeutic measure.

Although the role of hepatic local chemotherapy in unresectable liver metastases remained controversial, interest in the approach was renewed by two meta-analyses of published randomised data (10,11) (Table II). Both studies confirmed a statistically significant response advantage (41% of RR after HAI *versus* 14% after systemic chemotherapy). Survival analysis showed a statistical significant advantage for HAI, thanks to a high extraction ratio and solubility during the first hepatic pass (94-99%), when all trials were taken into account ($p=0.0009$). However, the advantage was not statistically significant, after the exclusion of two European studies ($p=0.14$) of Rougier and Allen-Mersh (12, 13). Definitive conclusions could not be achieved, because of the methodological limitations, such as the inadequate control arms, small number of patients, non-optimal choice and doses of chemotherapy infusion, or

early discontinuation of treatment on the trials. Moreover, some authors claimed that the absence of clear survival benefit with FUDR HAI chemotherapy was due to the absence of systemic disease control.

Kemeny *et al.* attempted to reduce the hepatotoxicity of FUDR, by adding dexamethasone and to increase the cytotoxicity of fluoropyrimidines with LV. This group reported a significant improvement of RR (56-78%, $p=0.03$) and MST (23-24.8 months $p=0.06$) (14). A study of comparison between FUDR/LV/dexamethasone HAI (days 1-14) and systemic 5-day 5FU/LV bolus (Mayo Clinic regimen) followed (Cancer and Leukaemia Group 8481). To avoid the methodological problems found in earlier trials, no cross-over was permitted, so those patients with systemic failure were discouraged from undergoing HAI therapies as salvage treatment. The statistical design was appropriate, but the improvements in systemic chemotherapy in this period and the realities of patient care, raised issues, as to whether the study design remained relevant.

To improve the systemic disease control, the sequential combination of FUDR HAI and systemic therapy with 5-day 5FU/LV bolus were also tested. Fifty-three percent RR and 25% SD were observed. The median TTP was 32 weeks (range 8-104 weeks), while the MST was 39 weeks (range 9-109 weeks) (15, 16).

The association of FUDR HAI with other new *i.v.* drugs administered in the neoadjuvant setting was subsequently explored in phase I trials. No definitive results have been obtained to date (17); optimal doses and schedule have yet to be found (18, 19). In the Kemeney *et al.* study (18), FUDR HAI and CPT11 *i.v.* were administered to 46 patients. The dose-limiting toxicity (DLT) was diarrhoea and neutropenia. The RR among all patients was 74%.

In another phase I trial, the same authors (19) treated 36 patients (89% previously treated) with 2 weeks HAI FUDR plus dexamethasone concurrently with systemic *i.v.* oxaliplatin plus CPT11 (group A) or oxaliplatin plus 5FU/LV (group B), every 28 days. The maximum tolerated dose (MTD) for patients in group A was oxaliplatin 100 mg/m^2, CPT11 150 mg/m^2 and FUDR 0.12 mg/kg x 30 ml divided by pump flow rate. The MTD for group B was oxaliplatin 100 mg/m^2, LV 400 mg/m^2, and 5FU 1,400 mg/m^2 by *c.i.* over 48 h, with the same FUDR dose as in group A. Grade 3 or 4 toxicities in groups A and B included diarrhoea (24% and 20%), neutropenia (10% and 7%), neurotoxicity (24% and 20%) and bilirubin more than 3 mg/ml (5% and 7%, respectively). The complete remission (CR) and partial remission (PR) rate was 90% for group A and 87% for group B. The MST was 36 and 22 months for groups A and B, respectively. Seven patients in group A were ultimately able to undergo liver resection. Combination therapy with HAI FUDR plus systemic oxaliplatin combinations may be safely administered to patients with colorectal cancer. The high RR (88%) and the possibility of conversion to resectability, despite disease progression (PD) on prior systemic regimens, suggest that these combinations should be evaluated in larger studies, as first- or second-line therapy in patients with hepatic metastases from colorectal cancer.

b) Second-line chemotherapy: Few data exist regarding HAI chemotherapy, as salvage treatment after the failure of a systemic therapy (20) (Table III). In the only phase II trial with high-dose Mitomycin C (MMC) added *via* the pump side port to HAI FUDR and dexamethasone, similar responses (73% *versus* 70%) and MST (23 *versus* 20 months) were reported in the chemotherapy-naive group (n=26) *versus* those previously treated (n=37). The second-line approach should still be considered as experimental, until it can be compared in randomised trials with alternative second-line systemic chemotherapy or with the best supportive care.

c) First-line chemotherapy: Prospective randomised trials comparing the advantages of chemotherapy with observation, only after a radical hepatic resection in colorectal cancer have not been carried out yet.

In a randomised study, Kemeny *et al.* (21) (Table III) treated 156 radically resected patients either with FUDR HAI, combined with systemic chemotherapy (5FU bolus with or without LV) or with systemic chemotherapy alone. In the first group, significant improvements in 2-year DFS (90% *versus* 60%, $p<0.001$), in 2-year OS (86% *versus* 72%, $p=0.03$) and in progression-free survival (PFS) (57% *versus* 42%, $p=0.07$) were observed. Adverse effects were similar in both arms, except for a higher frequency of diarrhoea and hepatic effects in the combined therapy group. Results seemed encouraging, but some authors reported bias in the study about FUDR doses, statistical methods, patient characteristics, trial design and interpretation of results.

Because of the undefined better treatment after hepatic metastases resection, Kemeny *et al.* (22) followed 75 radically resected patients either with FUDR HAI plus 5FU *c.i.* or without any further therapy. The 4-year TTP was 46% *versus* 25% in the control arm ($p=0.04$); the 4-year liver TTP was 67% *versus* 43% in the control arm ($p=0.03$). The data demonstrated that HAI and *i.v.* chemotherapy were beneficial in prolonging TTP and preventing recurrence, after hepatic resection of colorectal cancer. In light of these results, new combinations within HAI and *i.v.* administration have been performed and the results need to be confirmed (23, 24).

According to Kemeny *et al.* phase I/II trial (24), 96 patients were treated with six monthly cycles of HAI FUDR, plus dexamethasone, plus escalating doses of systemic CPT11. The MTD for combined systemic CPT11 and HAI FUDR was CPT11 at 200 mg/m^2 every other week and FUDR at 0.12 mg/kg x pump, volume/pump flow rate. The DLT were

Table III. *FUDR HAI infusion as first or second-line therapy.*

Authors	Drugs	No. of patients	DFS (%)	MST (months)
Second-line therapy:				
Fordy *et al.* (20)	FUDR HAI (floxuridine 0.25 mg/kg/day, d 1-14) + dexamethasone 20 mg + MMC HAI (15 mg/m^2, d 1, 29) q 28 d	63	n.r.	20
First-line therapy:				
After radical hepatic resection				
Kemeny *et al.* (21)	FUDR HAI (floxuridine 0.25 mg/kg/day, d 1-14) + dexamethasone 20 mg q 3 wks + *i.v.* 5FU 325 mg/m^2/day, d 1-5 ± LV 200 mg/m^2/day, X 6 cy *vs.* *i.v.* 5FU 325 mg/m^2/day, d 1-5 + LV 200 mg/m^2/day	156	90 *vs.* 60 (at 2 years) ($p<0.001$)	72.2 *vs.* 59.3
Kemeny *et al.* (22)	FUDR HAI 0.1-0.2 mg/kg/day, d 1-14+ 5FU 200 mg/m^2/day *c.i.*, d 1-14, X 4 cy *vs.* surgery alone	75	46 *vs.* 25 (at 4 years) ($p=0.04$)	63.7 *vs.* 49
After non-radical hepatic resection or in unresectable metastases				
Copur *et al.* (25)	FUDR HAI 60 mg/m^2/day + LV 15 mg/m^2/day *c.i.*, d 1-4 → 5FU 180 mg/m^2/day *c.i.* + oral LV 5 mg/m^2/day, d 1-21, q 6 wks, x 4 cy. Then 5FU 180 mg/m^2/day *c.i.* + ral LV 5 mg/m^2/day, d 1-21	43	n.r.	13
Pancera *et al.* (26)	FUDR HAI 0.25 mg/kg, d 3, + FOLFOX 4, q 5 wks	18	44.4	9

d=day; q=every; wks=weeks; *c.i.*=continuous infusion; n.s.=not significant; n.r.=not reported; cy=cycle; DFS=disease-free survival; MST=median survival time; FUDR=fluorodeoxyuridine; HAI=intra-arterial; 5FU=5-fluorouracil; LV=leucovorin; OXA=oxaliplatin; MMC=mitomycin C; FOLFOX4=oxaliplatin + 5FU bolus + 5FU *c.i.* + LV.

diarrhoea and neutropenia. With a median follow-up time of 26 months, the 2-year survival rate was 89%. All of the 27 patients, who were treated at the MTD, are alive. The regimen seems to give similar results to those obtained with 5FU/LV, but further studies need to assess, whether it also improves local control or decreases extrahepatic recurrences.

Studies to improve local and systemic control, were also carried out in those patients with unresectable or no radically resectable metastases (25, 26). In the Copur trial (25), 43 patients received 4-day FUDR HAI and LV followed, after 1 week rest, by 5FU *c.i.* and a fixed dose of oral LV. After 4 cycles, the patients continued with systemic 5FU/LV, until progression. The objective RR was 41%, the median TTP was 6 months and the MST was 13 months; these results were comparable to those achieved with more prolonged and frequent FUDR HAI. The approach was well tolerated. The treatment plan was short and non-responders after 1 cycle were not exposed to another HAI treatment, reducing this way toxicity and costs. Five inoperable patients became operable, suggesting a possible rule in neoadjuvant therapy for unresectable liver metastases.

To improve these results, FUDR HAI was also tested in combination with systemic CPT11 in the USA and Europe. At present, the rule of the combination with FOLFOX or FOLFIRI (which are more effective than 5FU/FA regimen) is actually debated (26). New studies are ongoing, but none have reported encouraging results. In the Pancera *et al.* study (26), FUDR HAI was associated with systemic FOLFOX4 in 18 patients with advanced colorectal metastases. PR of 38.8% and 5.5% stable disease (SD) were observed. One-hundred percent of resected patients and 80% of patients with advanced disease were alive after 4 months. Preliminary data of RR and OS were encouraging, but still not confirmed.

5-Fluorouracil HAI

a) Neoadjuvant therapy: HAI studies with 5FU/LV alone or in combination with other drugs (9, 27-31) demonstrated a RR similar to that obtained with HAI with FUDR, without major hepatic toxicity. No survival advantage was reported (Table IV).

Only when Muller *et al.* (32) treated 103 patients with short term 5FU HAI (regimen A) or with continuous circadian 5FU HAI (regimen B) plus LV, GM-CSF and chemo-embolisation, did the second arm seem to be more effective than the first, in

Table IV. *5FU HAI.*

Authors	Drugs	No. of patients	DFS (months)	MST (months)
Neoadjuvant therapy:				
Howell *et al.* (29)	FA 200 mg/m^2 *i.v.* over 2 h followed by 5FU 400 mg/m^2 HAI over 15 min, then 5FU 1600 mg/m^2 HAI over 22 h, d 1-2 q 2 wks	40	n.r.	19
Howell *et al.* (30)	5FU 1500 mg/m2 HAI plus FA 200 mg/m^2 *i.v.* for the first and last two h of the 5FU infusion, weekly for six wks q 8 *vs.*			
	FA 200 mg/m^2 *i.v.* over 2 h followed by 5FU 400 mg/m^2 HAI over 15 min, then 5FU 1600 mg/m^2 HAI over 22 h, d 1-2 q 2 wks	33 *vs.* 24	n.r.	19 (similar in both groups)
Lorenz *et al.* (31)	FA 500 mg/m^2 week HAI followed by 5FU 2,600 mg/m^2 HAI 24-h *c.i.* (later reduced to 2,200 mg/m^2)	50	12	22.3
First-line therapy after a curative resection:				
Lorenz *et al.* (33)	5FU HAI 1,000 mg/m^2 24-h *c.i.*, d 1-5, plus FA HAI 200 mg/m^2, d 1-5 as a short infusion *vs.* no CT	226	14.2 *vs.* 13.7	34.5 *vs.* 40.8 (ns) (the chance of detecting an expected 50% improvement in survival by the use of HAI was only 5%. Pt accrual was therefore terminated less than expected)
Tono *et al.* (35)	5FU HAI 500 mg/wk, d 1-4 x 6 wks *vs.* no CT	19	62.6 *vs.* 13.8 (p=0.045)	nr

d=day; q=every; wks=weeks; *c.i.*=continuous infusion; n.s.=not significant; n.r.=not reported; DFS=disease-free survival; RR=response rate; MST=median survival time; HAI=intra-arterial; 5FU=5-fluorouracil; LV=leucovorin; FA=folinic acid; OXA=oxaliplatin.

terms of RR (2.7% CR, 32.4% PR, 21.6% minimal response (MR), 12.7% SD, 16.2% non response (NR) *versus* 1% CR, 42.4% PR, 24.2% MR, 18.2% SD, 12.1% NR, respectively) and MST (17 *versus* 28 months, $p=0.0095$). These results have not been confirmed in other trials, to date.

b) First-line chemotherapy: HAI regional chemotherapy can be advantageous, when combined with hepatic resection or as a palliative therapy, but its actual role in a systemic disease as colorectal cancer is controversial. 5FU HAI produces, not only high intrahepatic drug concentrations (first-pass hepatic extraction less than 54%), but also significant systemic levels, due to excess drug spilling from the liver into the general circulation. Different schedules of HAI with 5FU have been investigated (33, 34) but, currently, only one randomised trial (35) seemed to suggest a benefit in terms of DFS ($p=0.045$) (1-, 2-, 3-year DFS of 77.8%, 77.8% and 66.7%, in the first arm on 9 patients, and 50%, 30%, and 20% in the control arm on 10 patients, respectively), with a median disease-free interval (DFI) of 62.6 months in the first arm *versus* 13.8 months in the control group. More numerous trials are necessary to confirm the activity and safety of 5FU HAI, as the first-line therapy in colorectal cancer patients.

CPT11 HAI. CPT11 is used as a systemic chemotherapeutic agent either in combination with 5FU or alone.

a) Second-line chemotherapy: In phase I studies (36-38) the MTD of CPT11 HAI was 25 mg/m^2/day and DLT were neutropenia and diarrhea; total body clearance of CPT11 was higher with HAI ($p=0.008$) than *i.v.* In a recent phase II study with CPT11 HAI (39) (Table V) a RR of 33% and a SD of 37.5% have been observed. More common toxicities were diarrhoea, anorexia, mild myelosuppression and alopecia. Data reported a good antitumour activity with low toxicity. The MST was not reported.

Table V. *New drugs via HAI administration.*

Authors	Drugs	No. of patients	RR (%)
Neyns *et al.* (39)	CPT11 HAI 20 mg/m^2/day, d 1-5, q 3 wks (second-line therapy)	10	33
Tanaka *et al.* (40)	chr CPT11 50-180 mg/m^2/day, d 1 + OXA 15-25 mg/m^2/day + 5FU 450-900 mg/m^2/day, d 2-5 (second-line therapy)	10	12.5
Tomirotti *et al.* (41)	OXA HAI 100 mg/m^2/day, 6-h infusion, d 1, + *i.v.* Machover/or de Gramont regimens, q 4 wk (first-line therapy)	12	16.6
Ducreux *et al.* (42)	OXA HAI 100 mg/m^2/day, 6-h infusion, d 1, + *i.v.* Machover/or de Gramont regimens, q 4 wk (first-line therapy)	26	64
Moosmann *et al.* (43)	FA HAI 200 mg/m^2, 1-h infusion + 5FU 600 mg/m^2, 2-h infusion, d 1-5, + oxaliplatin 62.5 mg/m^2, 4-h infusion, d 2 and 4	24	70.8

d=day; q=every; wks=weeks; chr=chronomodulated; RR=response rate; MST=median survival time; HAI=intra-arterial; 5FU=5-fluorouracil; OXA=oxaliplatin.

Since circadian chronotherapy improves tolerability and activity of *i.v.* infusion, and circadian clock genes regulate liver functions, Tanaka *et al.* (40) assessed the influence of 5-day chronomodulated CPT11 HAI, oxaliplatin and 5FU in 10 patients. Ten percent grade 3 neuropathy, 10% grade 3 alopecia, 40% grade 3 diarrhoea and leucopoenia, and 30% grade 3 nausea or vomiting were observed. Seventy-five percent SD were reported. The regimen was well tolerated and active but, to date, the advantage of CPT11 HAI has yet to be thoroughly analysed.

b) First-line chemotherapy: Phase II or III trials, on first-line chemotherapy with CPT HAI, have not yet been reported.

Oxaliplatin HAI

First-line chemotherapy: In order to increase RR and to decrease oxaliplatin toxicity, Tomirotti *et al.* (41, 42) (Table V) administered the drug *via* HAI. Twelve patients received oxaliplatin HAI and 5FU/LV *i.v.* according to the Machover or de Gramont regimens. Seventy-five percent SD was reported. Toxicity was mild and MST data were not reported.

More recently, Moosmann *et al.* (43) treated 24 patients with histologically documented colorectal cancer with exclusive liver metastasis, after surgery of the primary tumour. They were either chemonaïve (n=14) or had received an adjuvant treatment ≥6 months before the beginning of the study (n=10). Patients received HAI with folinic acid (FA) (200 mg/m^2, 1 h infusion) followed by 5FU (600 mg/m^2, 2 h infusion) on days 1 to 5, combined with oxaliplatin (62.5 mg/m^2, 4 h infusion) on days 2 and 4; dexamethasone 8mg per os (*p.o.*) was given 30 min prior and 2 h after application of oxaliplatin. Grade 3/4-toxicities included leucopoenia (19%), thrombocytopenia (10%), hyperbilirubinemia (10%), diarrhoea (5%) and abdominal pain (10%). The overall RR was 70.8%. CR was observed in 20.8% of patients, PR in 50% and SD in 12.5%. The median TTP was 8.8 months and the median OS reached 25.5 months. Four years after the onset of treatment, five patients (20.8%) were alive. Two patients (8.3%) had obtained partial liver resection and two patients (8.3%) were treated with radiofrequency ablation after remission had been achieved by the intrahepatic chemotherapy. Treatment was safe and highly effective in patients with exclusive liver metastasis.

Conclusion

Patients with isolated, potentially resectable colorectal cancer liver metastases should be treated surgically, to improve long-term survival, but only 10-15% of them actually have a limited and resectable disease; this rate may improve when resection is associated with local ablation. In the resected patients, while a systemic treatment has not yet been associated with any survival advantage, local post-operative treatment seems to improve OS, more than surgery alone (22, 35). Data from more numerous trials would help to confirm these results. HAI in combination with new intravenous drugs, could probably improve local RR and systemically control the disease and OS, more effectively.

In unresectable hepatic-only disease, regional therapies, such as cryosurgery or radiofrequency ablation have been considered, but in these cases more studies are needed as well, to demonstrate a real survival improvement. In those cases with extensive liver metastases, HAI has been administered as an alternative first-line and/or neo-adjuvant therapy to systemic chemotherapy with 5FU alone (but not to oxaliplatin or CPT11). A significant advantage in terms of RR has been observed, but a survival benefit has not yet been reported.

Increased vascular endothelial growth factor (VEGF) expression, the key regulator of normal and pathological angiogenesis, is associated with colorectal cancer liver metastases (44). The addition of VEGF-targeted drugs, such as bevacizumab (Avastin), to systemic chemotherapy, was shown to be significantly superior to chemotherapy alone in terms of objective tumour RR, PFS and OS in patients with metastatic colorectal cancer either in the frontline or, more recently, in the second-line setting, with no decline in chemotherapy-related toxicity (45, 46). Whether or not the antitumoral efficacy of bevacizumab combined with HAI is increased, could still be an interesting setting to analyse. Agents targeting EGFR are conceptually the same as those applied to VEGF. A major therapeutic advance, brought on by antibodies directed against EGFR in colorectal cancer, is attributable to cetuximab (Erbitux). Cetuximab is a monoclonal antibody impacting EGFR itself and has been approved, combined to irinotecan, in EGFR-positive metastatic colorectal cancer after progression, while under an irinotecan-based chemotherapy. One of the major current challenges regarding the clinical use of anti-EGFR drugs is to discover reliable predictors for identifying tumours sensitive to this targeted treatment and to evaluate these drugs in combination with others, both intrahepatically and systemically (47). The improvement of HAI-related RR and OS in association with the systemic or local administration of novel drugs could be a new frontier in the treatment of the advanced disease.

As second-line therapy, HAI should not be recommended outside clinical trials. Again, randomised studies are warranted to establish whether regional therapy leads to improved survival compared with systemic therapy alone or not (48).

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