

Heidelberger Symposium: Minireview

The role of floxuridine in metastatic liver disease

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Abstract

Liver metastases are mainly supplied by the hepatic artery. Sustained high levels of intratumoral drug are achievable with certain drugs given via the hepatic artery. Floxuridine (FUDR) is an ideal drug for hepatic arterial infusion (HAI) due to its short half life, steep dose response curve, high total body clearance, and high hepatic extraction. HAI FUDR has consistently shown higher response rates than systemic chemotherapy alone, and some studies have shown a survival advantage. HAI FUDR in combination with systemic chemotherapy has evolved over the years and may be used in palliative, neoadjuvant, and adjuvant settings. The dramatic responses observed with HAI FUDR plus modern era systemic chemotherapy offer the possibility of resection and cure in selected patients. The high hepatic extraction of FUDR limits systemic side effects. Toxicity includes biliary and gastrointestinal ulcers. [Mol Cancer Ther 2009;8(5):1015–25]

Introduction

Hepatic metastases are a frequent complication of colorectal cancer (CRC). In the United States it is estimated that there will be at least 148,810 new cases in 2008 with approximately 49,960 deaths (1). At diagnosis 20% to 25% of all patients will have synchronous liver metastases and at least another 60% of patients who develop metastatic disease will have liver metastases (2). The reason why the liver is the only site of metastases in more than one third of patients can be explained by the portal venous drainage of the colon and rectum to the liver. For more than 40 years fluoropyrimidines were the standard chemotherapy for metastatic CRC with response rates of 20% and median survivals of less than 12 months (3). Combinations of systemic 5-Fluorouracil (5FU) and leucovorin (LV) with oxaliplatin or irinotecan

as well as biologic agents such as bevacizumab and cetuximab have improved results, but the 2-year survival rate remains at about 40% (4–7). Surgical resection of liver metastases has become the end point for many trials with liver confined colorectal metastases as this modality can offer the possibility of cure. Upfront surgical resection in well-selected patients can result in 10-year survival rates of 20% to 22% and a significant chance of cure (2, 8, 9). Adjuvant chemotherapy is necessary as relapse rates are seen in 65% to 80% of patients and at least 50% of these relapses occur in the remnant liver (8). Neoadjuvant therapy (conversion therapy) can result in initially unresectable liver metastases becoming resectable and result in a similar 5-year survival rate as seen as for patients with initially resectable disease (10). This review will put in perspective where the use of hepatic arterial infusion (HAI) with floxuridine (FUDR) fits into the therapy of liver metastases as well as its use in the adjuvant and neoadjuvant settings.

Rationale for Hepatic Arterial Infusion of Floxuridine

Unique aspects of metastatic liver disease physiology explain the interest in liver-directed therapy. When liver metastases grow above 2 to 3 mm in size, the blood supply comes from the hepatic artery. Normal hepatic parenchyma derives its blood supply mostly from the portal circulation (11). Fluoropyrimidines have been the cornerstone of CRC chemotherapy for more than 50 years. Much work has been done looking at hepatic extraction of this drug class. 5FU and FUDR, the deoxyribonucleoside derivative of 5FU, are both pyrimidine antimetabolites, and both work through inhibition of thymidylate synthase. FUDR's principle mechanism of action is through 5-fluoro-2'-deoxyuridine-5'-monophosphate (FdUMP). However, there are significant differences in pharmacokinetic profile between these two drugs. Drugs that are extracted by the liver during first pass metabolism can result in high hepatic levels and low systemic concentrations thereby minimizing systemic toxicity. Increased local concentration depends on ratio of total body clearance to regional exchange (12). The best drugs for HAI are agents that have high hepatic extraction with conversion to inactive metabolites, high total body clearance, and short plasma half-life. If the drug is not rapidly cleared by the liver the regional advantage is lost because of systemic recirculation. 5FU has saturable, nonlinear pharmacokinetics, whereas FUDR displays linear kinetics. Therefore, total body clearance and hepatic extraction of 5FU decreases at high doses (13). Although oxaliplatin does not have superior pharmacokinetic characteristics for HAI, e.g., a long half

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life (15 to 19 hours), differences were seen in tumor versus healthy hepatic tissue in a ratio of 4.3, suggesting that oxaliplatin could be administered effectively and with minimal toxicity via the intra-arterial route (14, 15). Irinotecan is not suited for HAI as it is converted to an active metabolite, SN-38, in the liver after first-pass extraction, and systemic effects are seen. Total body clearance of irinotecan was higher with HAI versus systemic but the levels of SN38 were also higher (16). FUDR has therefore been the primary focus of research on drug therapy administered directly into the hepatic artery to treat liver metastases. Esinmenger estimated a 400-fold advantage for FUDR when given by the HAI route because of short half-life and extensive first pass extraction (17).

The rationale behind regional hepatic artery chemotherapy to liver is further explained by studies using labeled FUDR showing tumoral levels of FUDR 15 times higher with HAI versus portal vein infusion (18). In a randomized study comparing HAI versus portal vein infusion in patients with previously treated colorectal liver metastases, there were no responses in the portal vein infusion group whereas there was a 33% response in the HAI group (19). If patients whose tumor progressed on portal infusion of FUDR were switched over to HAI of FUDR, responses occurred, demonstrating that the same drug can produce different responses just by changing the route of administration.

Prolonged, controlled infusions of drug into the hepatic artery with long term catheter and artery patency were made possible by the development of implantable infusion pumps in the 1970s (see Fig. 1). Prior to the development of an internal pump, catheter and external pumps were used. Responses were good but catheter thromboses and bleeding complications were high (20). Studies have shown that implantable pumps can deliver chemotherapy for longer periods compared with surgical percutaneous catheter placement (115 versus 31 versus 25 days, respectively) (ref. 21). Modern implantable hepatic arterial pumps are placed at surgery, are usually fixed percutaneously in the left lower quadrant with the catheter inserted into the hepatic artery (Fig. 1), and can remain in place for years (with minimal complication rates) delivering chemotherapy, e.g., FUDR, continuously over a 2-week period followed by 2 weeks of glycerol or heparin saline as part of a 4-week cycle. The pump infuses drug at a constant rate owing to the expansion of an internal bellows exerting a constant pressure on an inner chamber that is filled with drug. The reservoir of the pump is filled percutaneously by accessing a subcutaneous septum using simple palpation and a refill kit. Reservoir volumes are 16 to 50 mL. To be suitable for pump placement patients must have no extra hepatic disease and have a reasonably normal hepatic arterial anatomy to the liver and its adjacent structures as seen on

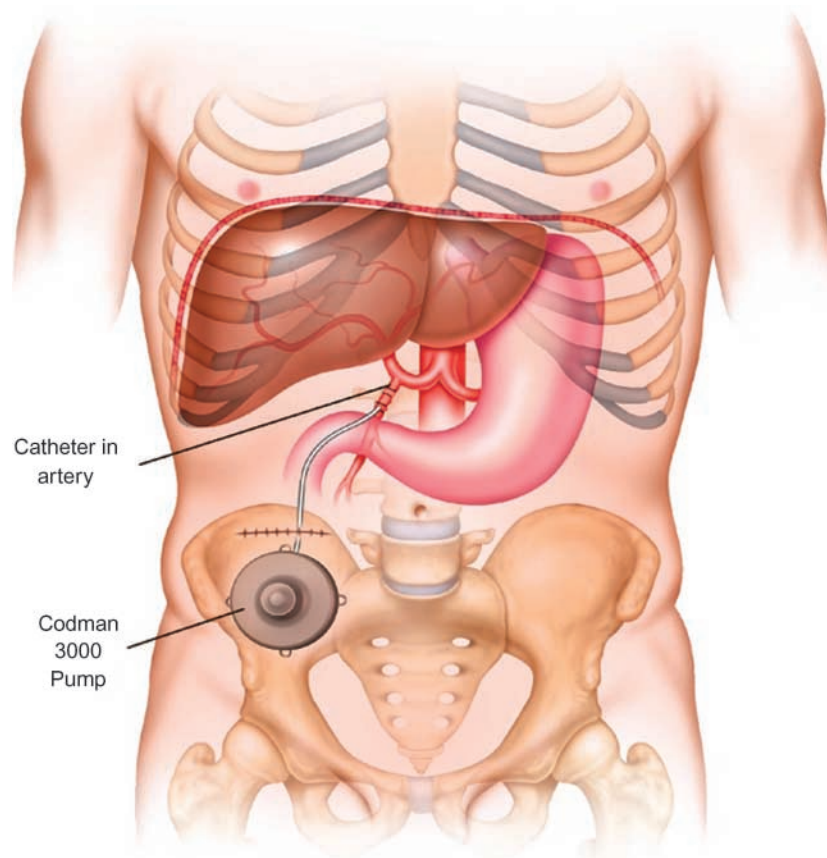


Figure 1. An implantable HAI pump with a catheter in the hepatic artery.

Table 1. Randomized trials of HAI for unresectable liver metastases

Study	Arms	n	Responses (CR+PR)	Median OS (months)
Kemeny et al. (26)	HAI FUDR	48	50%*	17
	IV FUDR	51	20%	12
Chang et al. (25)	HAI FUDR	32	62%*	17
	IV FUDR	32	17%	12
Hohn et al. (27)	HAI FUDR	67	42%*	16.5
	IV FUDR	76	10%	15.8
Wagman et al. (29)	HAI FUDR	31	55%*	13.8
	IV 5-FU	10	20%	11.6
Martin et al. (28)	HAI FUDR	39	48%	12.6
	IV 5-FU/LV	35	12%	10.5
Rougier et al. (30)	HAI FUDR	81	44%*	15
	IV 5-FU or BSC	82	9%	11
Allen-Mersh et al. (31)	HAI FUDR	51	–	13.5*
	IV 5-FU or BSC	49	–	7.5
Lorenz et al. (32)	HAI FUDR	54	43%*	12.7
	HAI 5-FU/LV	57	45%*	18.7
	IV 5-FU/LV	57	20%	17.6
Kerr et al. (33)	HAI FU/LV	145	22%†	14.7
	IV 5-FU/LV	145	19%	14.8
Kemeny et al. (34)	HAI FUDR/Dex	68	48%*	24*
	IV 5-FU/LV	67	25%	20

NOTE: Overall survival (OS) calculations are based on intention to treat.

Abbreviations: CR, complete response; PR, partial response.

*Statistically significant difference ($P < 0.05$) compared with control group.

†Responses in this trial were calculated at a single time point (12 wk) in 77 HAI and 108 control patients.

computerized tomographic (CT) angiography. In some patients, accessory arteries supplying the liver may be ligated and still allow perfusion of the liver by one catheter. The portal vein must be patent (see section on Toxicity of HAI FUDR below for a detailed discussion on pump complications rates, etc.) FUDR is ideal for administration via an implantable pump system as it is stable at body temperature, is soluble in low volumes, and is compatible with the implantable pump materials such as titanium, silicone, rubber, and polyurethane. Systemic chemotherapy can be given concurrently with HAI FUDR. This review will focus on the role of intra-arterial FUDR in the treatment of liver-confined metastatic CRC and highlight its evolving role in combination with modern systemic chemo-biologic therapy.

First Line Therapy in Unresectable Liver Metastases

Early studies using FUDR as continuous HAI produced median response rates of 45% and median survival of 17 months (22–24). These results stimulated a series of phase III trials that compared HAI FUDR or 5FU/LV to systemic FUDR or 5FU/LV. Ten prospective randomized phase III trials have been published (25–34) (see Table 1). It is difficult to make definitive conclusions from these trials because there are a number of design flaws evident especially in the first seven trials. (1) Numbers of patients were small. To show a 50% increase in median survival, a study would need 100 patient deaths per study arm to provide a power of 82%. None of the first seven randomized trials up to 1994

were large enough to answer this question (25–31). (2) A crossover design was allowed in the Memorial Sloan Kettering Cancer Center (MSKCC) (ref. 26), Northern California Oncology Group (NCOG) (ref. 27), and City of Hope (28) studies in which patients with progression of disease in the systemic arms were allowed to crossover to HAI treatment. (3) In some studies, e.g., the Mayo and NCOG studies, some patients had extrahepatic disease and were included, therefore it is difficult to show a survival advantage if no systemic drug is administered (25, 27). (4) A number of patients who were assigned to the HAI arms did not receive treatment and were included in survival analysis (32, 33). (5) A lack of predetermined dose-reduction schema may have led to greater toxicities and fewer cycles of therapy (32). All of these studies, however, showed a higher response rate for the HAI treatment arms versus the systemic groups (42% to 62% versus 9% to 21%). A significant overall survival benefit between 4 to 7 months was seen in two trials (30, 31). Two meta-analyses of the first seven trials were done, and both of these showed an increase in response and a survival advantage (35, 36). The two more recent European trials conducted had similar serious design flaws, e.g., only 70% patients in the HAI arm received treatment, and crossover to the HAI arm was allowed (32, 33). These studies had a different focus when compared to the American studies, e.g., in one study 5FU/LV was used via HAI and not FUDR (33), and in the other study a fixed dose of FUDR was used via a port (a subcutaneous device accessing the hepatic artery and requiring an external pump) not an implantable pump (32).

The Cancer and Leukemia Group B (CALGB) study of 2006 randomized patients to HAI FUDR versus systemic 5FU/LV and included dexamethasone (Dex) in the HAI arm in order to decrease FUDR toxicity (34). Kemeny and colleagues had shown the efficacy of this strategy previously (37, 38). In a randomized study of HAI FUDR/Dex versus HAI FUDR, there was a decrease in biliary toxicity and a trend toward increased overall survival with the addition of Dex (median survival, 23 months versus 15 months, respectively, $P = 0.06$) (ref. 37). In a phase II study HAI FUDR/Dex showed a response rate of 78% and a median overall survival of 24.8 months in previously untreated patients. Only 3% of patients developed biliary sclerosis, which was significantly less than the 21% biliary sclerosis rate seen in an HAI FUDR/LV study without Dex (38). The CALGB study was a well designed study in which no crossover was allowed, only 13% of patients in the HAI arm were not treated, and a pump was used instead of a port. The HAI group had a significant increase in survival (24.4 versus 20 months, $P = 0.0034$). The time to hepatic progression was superior in the HAI arm (9.8 versus 7.3 months, $P = 0.034$), but the time to extrahepatic progression was better in the systemic arm (7.7 months versus 14.8 months, $P = 0.029$). Toxicities more frequent in the systemic arm included diarrhea, neutropenia, and stomatitis ($P < 0.05$). In the HAI group biliary elevations more than 3 mg/dL were seen in 18.6% versus 0% in the systemic arms ($P < 0.01$). Four patients required biliary stents (three placed more than 1 year after starting HAI therapy). A quality of life assessment showed better physical functioning in the HAI group at 3 months, which was maintained at 6 months ($P = 0.038$) and reported fewer symptoms in the HAI group ($P = 0.017$). The CALGB study shows that regional therapy with FUDR/LV/Dex alone can improve survival over systemic 5FU/LV with a survival rate similar to that seen with more modern systemic agents. The 1- and 2-year survivals of 82% and 51% compare favorably with modern systemic combinations, e.g., irinotecan/FU/LV/bevacizumab (6), Oxaliplatin/5FU/LV (7), and irinotecan/5FU/LV (5). The use of HAI alone, however, in a new meta-analysis using the

old flawed studies did not show an increased survival (39), therefore it may be more appropriate to ask in the modern chemotherapy era if the combination of HAI FUDR/Dex with systemic chemotherapy is more useful than systemic therapy alone. In the section on HAI FUDR plus systemic chemotherapy (second line therapy) we discuss studies examining the combination of HAI FUDR and modern systemic chemotherapy in previously treated patients. A subset of patients in these studies was chemo-naïve and HAI FUDR added to either systemic oxaliplatin and/or irinotecan-based regimens produced a median survival of 50.8 months in patients with initially unresectable liver metastases (40).

Adjuvant HAI FUDR after Liver Resection

Long term survival from colorectal liver metastases is possible with resection of disease allowing at least 30% of patients to be alive at 5 years (8). However, recurrences, both intrahepatic and extrahepatic, commonly occur (41). Risk models have been developed that predict recurrence and help decide which patients would benefit from adjuvant therapy (8). It is estimated that up to 70% of patients will develop recurrence within the first 3 years postresection, with about 30% to 60% of the recurrences in the remnant liver (42). Systemic adjuvant chemotherapy is now increasingly accepted as a standard of care even though it has been difficult to show a survival advantage with 5FU-based adjuvant therapy (43, 44). As small residual disease is the most likely cause of liver recurrence, the role of adjuvant HAI may be useful. The hepatic arterial supply of tumors larger than 3 mm provides a rationale for HAI in this setting. However, the risk of disease progression outside the liver suggests HAI should be combined with systemic therapy. In a patient who has had the primary colorectal tumor resected, micro-metastatic disease smaller than 3 mm may be a consideration, but in a patient with resected liver metastases, remaining disease may be larger than 3 mm and therefore HAI rather than portal vein infusion should be considered.

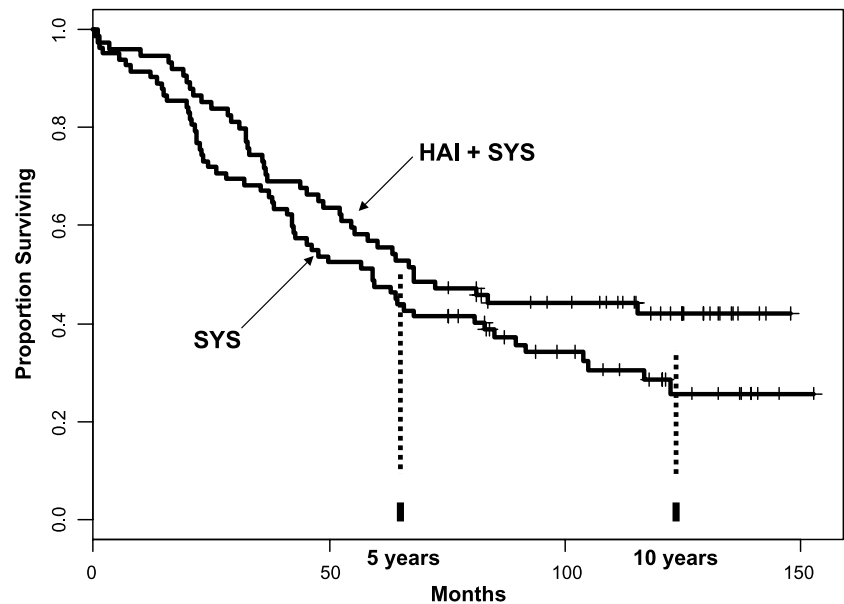
Table 2. True randomized trials of adjuvant HAI FUDR

Studies	Survival	n	% 2 Year		% 5 Year		P
			HAI	SYS	HAI	SYS	
MSKCC (51)	Hepatic progression-free	156	90	60	75	40	0.0001
ECOG (50)		75	75	50*	70	40*	0.0001
Lorenz (46)		186	Median		43/27*		NS
Lygidakis (49)		122	92	75	73	60	0.0001
MSKCC (51)	Disease-free	156	55	40	40	30	0.02
ECOG (50)		75	60	40	40	20*	0.03
Lorenz (46)		186	Median		20/12.6*		NS
Lygidakis (49)		122	66	48	60	35	0.0002

Abbreviations: SYS, systemic treatment; NS, not significant.

*No treatment in control arm.

Figure 2. MSKCC adjuvant trial of HAI FUDR + systemic 5FU/LV versus systemic 5FU/LV alone (51). Kaplan-Meier curves showing overall survival at 5 and 10 y.



Several trials using HAI treatment in the adjuvant setting have been reported (22, 45–51) (see Table 2 for true randomized adjuvant HAI trials). The MSKCC trial by Kemeny and colleagues randomized 156 patients to HAI FUDR/Dex combined with systemic (SYS) 5FU/LV ($n = 74$) versus SYS 5FU/LV alone ($n = 82$) postresection (47). Both groups were equally matched with respect to base-line characteristics, including number of liver metastases, the type of disease (metachronous versus synchronous), Duke's stage of disease, preoperative carcinoembryonic antigen levels, the percentage of liver involvement, the number who underwent trisegmentectomy, the number with positive surgical margins, and prior treatment history. Treatment duration was 6 months, i.e., HAI FUDR/Dex was given for 2 weeks followed by 2 weeks of heparin saline (a 1-month cycle). Systemic treatment was 5 days of FU/LV every month. The endpoint of the study was an increase in 2-year survival. Historical data in this setting showed a 2-year survival of 50% to 72% and a 2-year recurrence rate of 65% to 80% (52). The HAI plus SYS group had a 2-year overall survival of 86% versus 72% for SYS alone ($P = 0.03$) and hepatic disease free survival of 90% versus 60% ($P < 0.001$), respectively. The 2-year disease free survival in the HAI + SYS group was 57% versus 41% in the SYS arm ($P = 0.07$). Updated results from this study report a 10-year survival rate of 41% for patients in the HAI + SYS arm versus 27.2% for those in the SYS arm ($P = 0.10$) (see Fig. 2). Overall progression-free survival is now 31.3 months in the HAI + SYS group versus 17.2 months in the SYS group ($P = 0.02$). The median hepatic progression-free survival has not yet been reached in the HAI plus systemic group, and is 32.5 months in the systemic only group (51).

The Eastern Cooperative Group (ECOG) and South-Western Oncology Group (SWOG) randomized patients to surgical resection of hepatic metastases followed by HAI FUDR and SYS 5FU versus surgery alone. The endpoint in

this study was disease-free survival and this was accomplished. Of the assessable patients (75/109), the 4-year disease-free survival was improved in the HAI group (46% versus 25%, $P = 0.03$), and a trend toward a greater 4-year overall survival was seen (62% versus 53%, $P = 0.06$) (ref. 50). Lygidakis and colleagues reported a randomized trial comparing liver resection alone with liver resection followed by HAI of chemo-immunotherapy and showed a significant improvement in mean survival with adjuvant HAI chemo-immunotherapy (median survival of 20 months for the HAI arm versus 11 months for the surgery alone arm, $P = 0.001$) (ref. 45). In another randomized study Lygidakis and colleagues compared "adjuvant" HAI chemo-immunotherapy (C-mitomycin, FU, and Il-2) plus systemic chemotherapy versus intravenous chemo-immunotherapy alone after liver resection. An overall survival advantage was seen at 2 years (92% versus 75%) and 5 years (73% versus 60%) for (HAI + SYS) chemo-immunotherapy versus SYS immunotherapy, respectively (49).

In one of the German studies, patients were randomized to HAI 5FU/LV via a port or to surgery alone. In the treatment arm, 11% of patients received no hepatic treatment, 5% were not resected, and only 30% completed chemotherapy. At an 18-month interim analysis, no improvement in the median time to progression was seen. But in treated patients, median progression-free survival in the liver was 45 months for the HAI + SYS group and 39.7 months in the control group, and median time to progression was 20 and 13 months, for the HAI + SYS versus control groups, respectively (46).

Using modern systemic therapy in combination with HAI has produced good results. A phase I/II study of HAI FUDR/Dex in combination with systemic irinotecan in patients postliver resection gave a 2-year survival of 89% at a median of 26 months follow-up (53). A phase I trial of HAI FUDR/Dex in combination with systemic oxaliplatin and

5FU/LV after resection of liver metastases showed a 3-year survival of 89%, median survival not reached (54). In a recent review of more than 1,000 patients who underwent liver resection at our institution, Ito and colleagues showed in a multivariate analysis that one of the significant factors to improve survival was postoperative HAI therapy (55). The median overall survival was 68 months with HAI therapy and 50 months for those that did not receive HAI ($P = 0.0001$). Studies are currently ongoing in MSKCC adding bevacizumab to systemic chemotherapy combined with HAI FUDR in an attempt to prolong hepatic and extrahepatic progression-free rates further. Another retrospective review from our institution by Tomlinson and colleagues reported 612 patients who had liver resection over the period 1985 to 1994. The 10-year overall survival was 38% for those patients who received adjuvant HAI FUDR and 15% for those patients who did not ($P < 0.0001$) (ref. 9). House and colleagues studied the use of HAI in combination with modern systemic chemotherapy given in the adjuvant setting after liver resection. Between 2001 to 2005, 125 patients who underwent liver resection followed by HAI FUDR/Dex plus FOLFOX or FOLFIRI were compared with 125 consecutive patients who received adjuvant FOLFOX or FOLFIRI after liver resection. With a median follow-up of 43 months, the 5-year hepatic free survival was 75% in the HAI group versus 52% in the systemic arm ($P = 0.0005$). Overall survival at 5 years was 72% in the HAI group versus 52% in the systemic group ($P = 0.004$) (ref. 56).

In summary, the role of HAI FUDR in combination with systemic FU, in the adjuvant setting after liver resection, has been shown to be of benefit in terms of both hepatic-free survival and progression-free survival in three out of four randomized studies. HAI FUDR/Dex in combination with modern systemic chemotherapy, in small studies, seems to show further improvement. There is a need for randomized trials to define the role of HAI FUDR with or without modern systemic chemotherapy in the adjuvant setting after liver resection.

HAI FUDR Plus Systemic Chemotherapy (Second Line Therapy)

Responses to HAI FUDR combined with systemic chemotherapy are seen in patients who have been previously treated with systemic chemotherapy. Second-line systemic chemotherapy in advanced CRC typically produces response rates less than 40% and median overall survival less than 14 months (57). In patients with unresectable liver metastases from CRC, adding HAI FUDR/Dex to systemic irinotecan produced response rates of 74% with a median survival of 20 months (58). All 46 patients were previously treated with chemotherapy including 16 patients with previous irinotecan. Dose-limiting toxicities were diarrhea and myelosuppression. HAI FUDR/Dex with systemic oxaliplatin combinations in a phase I study of 36 patients with unresectable liver metastases from CRC was evaluated in two groups (59). Group A received HAI FUDR/Dex and systemic oxaliplatin plus irinotecan, and group B received HAI

FUDR/Dex plus systemic oxaliplatin and 5-FU/LV. The majority of patients had received prior chemotherapy (89%). Response rates were 90% for group A and 87% for group B. Seven patients in group A ultimately went for liver resection. Shiatra and colleagues used HAI 5FU and systemic irinotecan in pretreated patients. Objective response rates were 76.5%, and median survival time was 20 months (60). In a retrospective series, Gallagher and colleagues reported on the use of HAI FUDR/Dex in combination with systemic irinotecan in heavily pretreated patients who had unresectable disease. All patients had received previous oxaliplatin and 28% had prior irinotecan (61). Response rate for 39 patients was 44%, and median overall survival from the time of initiation of HAI was 20.1 months, whereas it was 32 months from the initiation of treatment for metastatic disease. Eighteen percent of patients proceeded to resection or ablation. In an updated series, 49 patients with unresectable liver metastases from CRC were treated with HAI FUDR/Dex plus systemic oxaliplatin/irinotecan. Patients were clearly unresectable as 98% had bilobar disease and 85% had tumors that bordered vessels. Response rate was 93%, and overall survival was 50.8 months in those patients who were chemo-naïve and 35 months in those patients previously treated (40).

Even in heavily pretreated patients with advanced CRC with liver-confined metastases, HAI FUDR can increase response rates and resection rates when combined with modern systemic chemotherapy. Future randomized trials should compare HAI + systemic chemotherapy to systemic chemotherapy alone in order to assess the additional value of HAI therapy in converting patients with hepatic metastases to resectability.

Neoadjuvant HAI FUDR

In patients with unresectable disease it is possible to decrease tumor size with neoadjuvant (conversion) chemotherapy, and perhaps biologic therapy, and resectability rates of 15% to 30% can result in patients with previously unresectable liver metastases from CRC (62, 63). HAI has consistently shown higher response rates than systemic chemotherapy (discussed above) and therefore may help increase the ability to get to resectable disease. HAI FUDR/Dex combined with oxaliplatin- and irinotecan-based regimens can produce resectability rates of up to 47% with no additional toxicity in patients who were definitely unresectable at presentation (40, 61). Most of these patients (53%) received prior systemic therapy. The benefit of HAI therapy given in a neoadjuvant setting has been also been highlighted by Auer and colleagues. Radiologic complete response of liver metastases in patients treated with HAI FUDR is more likely to represent a true complete response when compared to systemic neoadjuvant chemotherapy (42% versus 14%, respectively, $P \leq 0.001$).¹ The

¹ R.C. Auer, R.R. White, N. Kemeny, et al. Predictors of a true complete response among disappearing liver metastases from colorectal cancer following chemotherapy, submitted for publication.

benefit of HAI in the neoadjuvant setting has also been reported with the use of other drugs besides FUDR. Several studies report using neoadjuvant HAI oxaliplatin combined with systemic 5FU increasing response and resectability rates (14, 64, 65).

Neoadjuvant systemic chemotherapy can result in higher complication rates when compared to immediate surgery for resectable liver metastases. Nordlinger and colleagues report a reversible complication rate of 24% versus 13% (66). Rates of adverse liver effects with systemic chemotherapy include steatosis (5FU and irinotecan, 20%), sinusoidal dilatation (oxaliplatin, 19%), and steatohepatitis (irinotecan, 20%) (ref. 67). In the two series from our institution, the addition of HAI FUDR/Dex to systemic chemotherapy did not result in more frequent complication rates from liver resection (40, 61). In the updated series by Kemeny and colleagues, significant postoperative complications occurred in two patients (9%) (hematoma and a noninfected fluid collection; both had interventional radiology drainage). Three patients required biliary stenting, 4 years, 3 years, and 8 months after study completion, and all had progression of disease prior to stenting (40).

Toxicity of HAI FUDR

The toxicity of HAI can be mechanical, chemical, or a combination of both. Surgically implantable pumps have low complication rates. Allen and colleagues reported on HAI pump complications in 544 patients throughout the course of treatment. Complications within the first 30 days of placement were more likely to be catheter occlusions or arterial thromboses and less likely to be salvaged (68). Overall rates of pump failure were low being 9% at 1 year and 16%

at 2 years. The overall pump complication rate was 22%, and the majority of these complications were salvaged with 80% remaining functional for at least 2 years. All patients have a nuclear medicine macro-aggregated albumin scan before the pump is used to assess whether the liver is being perfused or if there is extrahepatic perfusion via side branches of the gastroduodenal artery. If there is misperfusion to the stomach or duodenum, ulceration or diarrhea can result. In contrast to systemic chemotherapy, myelosuppression, nausea, and vomiting do not occur with HAI FUDR. Hepatotoxicity from HAI depends on the drugs being used and the duration of treatment. The hepatic artery supplies the bile ducts, and therefore toxicity of HAI FUDR can be biliary. Elevation in liver enzymes or bilirubin is the most common toxicity associated with HAI therapy, occurring in 42% of patients in the randomized trials for unresectable liver disease reported above (69). Increase in transaminase levels is not uncommon (up to 70% of cases) and can be an early sign of biliary damage (70). Increases in bilirubin and alkaline phosphatase are more serious. Up to 29% of cases before the addition of Dex to the pump developed strictures of the bile ducts (biliary sclerosis) (ref. 38). In the adjuvant pump studies at our institution, a larger than twofold increase in alkaline phosphatase was seen in 27% to 43% of cases. An increase in bilirubin greater than 3.0 mg/dL was seen in 6% to 19% of cases with biliary stents required in 3% to 8% of cases. Transaminases increased by 37% to 59% (47, 53, 59). In the recently updated study by Kemeny and colleagues, HAI FUDR/Dex was combined with oxaliplatin and irinotecan over a 5-week cycle (40). Toxicities during the first two cycles were: grade 3 diarrhea (33%), grade 3/4 alkaline phosphatase (15% and 11%, respectively), grade 3/4 AST (19%), grade 3 bilirubin (4%),

Table 3. Dose reductions for HAI FUDR

Liver blood test		Lower reference range	Upper reference range	FUDR dose
AST	Ref*	≤50 U/L	>50 U/L	
	Current value [†]	0 to <3 × ref	0 to <2 × ref	100%
	3 to <4 × ref	2 to <3 × ref	80%	
	4 to <5 × ref	3 to <4 × ref	50%	
	≥5 × ref	≥4 × ref	Hold	
If held, restart when:	<4 × ref	<3 × ref	50% off last dose	
Alk Phos	Ref*	≤90 U/L	>90 U/L	
	Current value [†]	0 to <1.5 × ref	0 to <1.2 × ref	100%
	1.5 to >2 × ref	1.2-1.5 × ref	80%	
	≥2 × ref	≥1.5 × ref	Hold	
	If held, restart when:	<1.5 × ref	<1.2 × ref	25% off last dose
Total bilirubin	Ref*	≤1.2 mg/dL	>1.2 md/dL	
	Current value [†]	0 to <1.5 × ref	0 to <1.2 × ref	100%
	1.5 to <2 × ref	1.5 to <2 × ref	1.2 to <1.5 × ref	50%
	≥2 × ref	≥2 × ref	≥1.5 × ref	Hold
	If held, restart when:	<1.5 × ref	<1.2 × ref	25% off last dose

Abbreviations: AST, aspartate transaminase; Alk Phos, alkaline phosphatase; ref, reference value.

*Reference value is the value obtained on the day patient received the last FUDR dose.

[†]Current value is that obtained at pump emptying or on the day of planned treatment (whichever is higher).

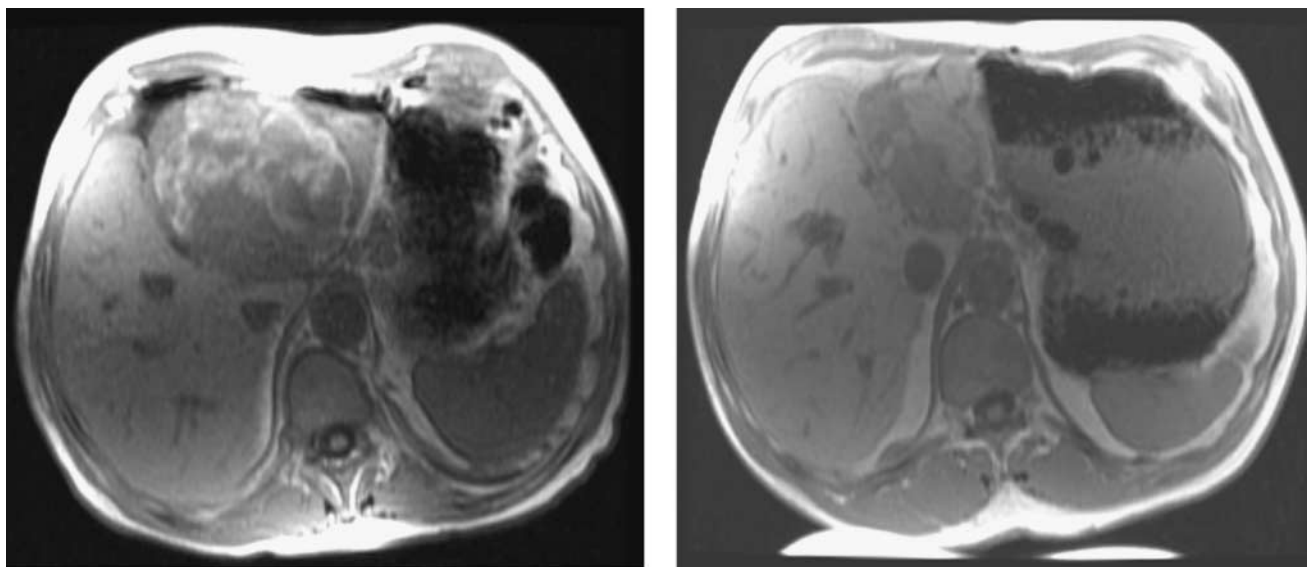


Figure 3. Unresectable HCC (left side) pre-HAI FUDR/Dex. Partial response (55% reduction per World Health Organization Criteria) posttreatment with HAI FUDR/Dex (right side). Response duration: 9 mo.

and grade 3/4 neutropenia (19% and 4%, respectively). Late toxicity (after the first two cycles) included grade 3 diarrhea (7%), grade 3 or 4 alkaline phosphatase (22% and 11%, respectively), grade 3/4 AST (7%), grade 3/4 neutropenia (15% and 11%, respectively), and neurotoxicity (19%). Thus an algorithm for dose reductions based on liver blood tests has been devised, and FUDR can be dose adjusted accordingly (see Table 3). As mentioned above, the addition of Dex to FUDR reduces biliary toxicity (37, 38). HAI FUDR/Dex is administered every month (if enzymes are normal). The pump continuously infuses drug, and after 2 weeks the reservoir is emptied and then refilled with heparin saline or glycerol, which then infuses over a further 2 weeks. If a patient develops an elevated bilirubin, chemotherapy is held, and Dex with heparinized saline is placed in the pump. If the bilirubin still does not normalize, then an ERCP can be done to evaluate for focal strictures that may respond to dilatation. When the pump is not in use, glycerol is inserted every 6 to 8 weeks to keep the catheter patent. If the pump is no longer required it can be surgically removed by a small incision and the catheter in the hepatic artery is cut off from the pump and left in place.

HAI and Non-CRC Liver Metastases

Liver metastases are much less common in non-CRC. Some trials have been done in breast cancer with liver metastases only after progression on systemic therapy. Drugs used via HAI include cisplatin/vinblastine, etoposide/cyclophosphamide, FU/doxorubicin/mitomycin, and FUDR. A study of 15 patients using HAI FUDR + mitomycin-c in patients with metastatic breast cancer with chemotherapy refractory disease showed a partial response rate of 53% and overall survival of 18 months from the time of HAI initiation (71).

In hepatocellular carcinoma (HCC), HAI FUDR has been used alone, in combination with leucovorin + doxorubicin + cisplatin (72), and in combination with mitomycin-c/interferon (73). Response rates of 41% to 54% were seen, and median overall survival of 15 months ($n = 29$) was reported in the HAI FUDR/LV/doxorubicin/cisplatin study by Patt and colleagues (72). At MSKCC, a study of 34 patients with unresectable HCC ($n = 8$) and intrahepatic cholangiocarcinoma (ICC) ($n = 26$) treated with HAI FUDR/Dex alone, partial responses were seen in 47.1% of patients and median survival was 29.5 months (see Fig. 3). One patient with ICC went on to resection and had a complete pathological response. Median duration of response was 11.9 months (4.1 to 14.7 months). Median time to progression for all patients was 7.4 months. With a median follow-up of 35 months, 1- and 2-year survival is at 88% and 67%, respectively. Treatment was well tolerated with no patients requiring biliary stenting, and no significant diarrhea or neutropenia was seen. Preliminary results with Dynamic Contrast Enhanced Magnetic Resonance Imaging show that changes in tumor perfusion characteristics may predict treatment response earlier and correlate with probability of response in patients with ICC or HCC.²

Conclusion

HAI FUDR both alone and in combination with systemic chemotherapy has resulted in high response rates, longer hepatic progression-free survival, and increasing resection rates for unresectable liver disease from CRC. Fluoropyrimidine

² W.R. Jarnagin, L.H. Schwartz, M. Gönen, et al. Regional chemotherapy for unresectable primary liver cancer: Results of a phase II clinical trial and assessment of DCE-MRI as a biomarker of survival, submitted for publication.

have been the cornerstone of CRC treatment for more than 50 years. A good way to deliver these drugs, especially FUDR, to a patient with liver metastases from CRC is via HAI. Modern implantable HAI pumps have low rates of immediate and long term complications. The combination of HAI FUDR with modern systemic chemotherapy is an effective way to treat such patients with liver metastases. In the adjuvant setting HAI FUDR and systemic chemotherapy combinations can increase disease-free survival and hepatic disease-free survival. The studies were not powered to look at overall survival. Consideration should be given to placing an HAI pump at the time of liver resection and treating with adjuvant HAI FUDR plus systemic chemotherapy. If the liver disease is unresectable and a trial of systemic chemotherapy with or without biologic agents, e.g., bevacizumab or cetuximab, fails to make the liver resectable, then HAI plus systemic chemotherapy should be considered. HAI FUDR/Dex combined with modern systemic chemotherapy has a role in the treatment of liver metastases from CRC.

Disclosure of Potential Conflicts of Interest

N. Kemeny: recipient of research grants from Sanofi-Aventis, Pfizer, and Johnson&Johnson; advisor to Sanofi-Aventis. No other potential conflicts of interest were disclosed.

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