PREFACE

Regional antineoplastic drug administration is not a new concept, having been examined since the earliest days of the modern chemotherapeutic era. For example, nitrogen mustard and hemisulfur mustard were administered by the intraperitoneal route in the 1950s as a strategy to treat malignant effusions (*1,2*), while during the same time period alkylating agents were delivered by direct intraarterial instillation to treat localized tumor masses (*3*).

Over the past several decades much has been learned regarding both the potential benefits (e.g., improvement in local symptoms and quality of life, prolongation of progression-free and overall survival) and the toxicities associated with regional antineoplastic drug delivery.

Local side effects of treatment include both the direct effects of the high concentrations of drug in contact with the infused/instilled body compartment [e.g., adhesion formation following intraperitoneal therapy (*4*), blindness following intra-carotid artery delivery (*5*), biliary sclerosis following intrahepatic artery infusions (*6*)] and the complications associated with the actual drug administration (e.g., infection of catheters and bleeding following intraarterial infusion).

In a number of specific malignant disease settings, this therapeutic strategy has become the "standard of care" in patient management. Examples include the use of intravesical therapy of localized bladder cancer (*7*), and intrathecal or intraventricular antineoplastic drug delivery for treatment of meningeal leukemia (*8*). In both situations regional therapy has been established as a highly effective treatment approach.

In other areas, such as the use of intraperitoneal chemotherapy in the management of ovarian cancer, accumulating data have strongly suggested an important role for the strategy in a subset of individuals with the malignancy. Two recently reported randomized clinical trials have demonstrated that, compared to the intravenous delivery of cisplatin, the intraperitoneal administration of the agent as initial chemotherapy of small volume residual disease results in an improvement in both progression-free and overall survival (*9,10*).

Finally, promising and highly innovative approaches to the management of malignant disease that employ regional drug delivery have been reported during the past several years from a number of major research centers throughout the world. These include the direct delivery of antineoplastic agents into body cavities (peritoneal cavity, pleura, pericardium, bladder, meninges) and arterial blood vessels, utilizing both cytotoxic and biological agents.

In *Regional Chemotherapy: Clinical Research and Practice* we have been extremely fortunate to assemble many leading clinicians and clinical investigators in the rapidly expanding arena of regional antineoplastic drug delivery from around the world, to contribute to a discussion of the current state-of-the-art, as well as new developments in this important area of oncologic care and research.

Although some of the approaches to be discussed remain highly experimental, it can reasonably be hoped and anticipated that many of these imaginative and innovative strategies will ultimately be recognized as "standard treatment" for patients with malignant disease confined to specific regions of the human body.

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2 Intrahepatic Chemotherapy for Metastatic Colorectal Cancer

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CONTENTS

1. INTRODUCTION

Colorectal cancer (CRC) is the fourth most common malignancy in the United States *(1)*. Approximately 130,000 new patients will be diagnosed with this cancer in 1999. It is the second leading cause of cancer death, with 55,000 patients expected to die of it. Most patients die of metastatic disease. The vast majority of them have liver as the dominant site of metastases *(2)*. Approximately 30% of patients with metastatic CRC have disease confined to the liver; 10–25% of patients undergoing resection of primary CRC have synchronous hepatic metastases.

Potentially curative resection is possible in a minority of patients with hepatic disease. Systemic chemotherapy produces response rates of 15–30%, with median survival of 10–12 mo. It is estimated that 30,000 patients are candidates for regional hepatic therapy each year. Thus, the impact of this malady is substantial.

The anatomic and pharmacokinetic advantage of intraarterial chemotherapy in patients with hepatic disease makes it an attractive therapeutic option. Regional hepatic arterial infusion (HAI) chemotherapy can be administered via a hepatic arterial port

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or a percutaneously placed intraarterial catheter connected to an external or totally implantable pump. Operative complications and hepatobiliary toxicity have been a hindrance to the widespread use of regional intrahepatic therapy. However, improvements in surgical technique and newer chemotherapy combinations have decreased the complication rate of this treatment modality.

2. RATIONALE FOR HAI

The rationale for HAI chemotherapy is based on both anatomic and pharmacologic factors. Even though colorectal metastases appear to migrate to the liver via the portal vein, they derive their blood supply almost exclusively from the hepatic artery, once they are greater than 1 cm in diameter *(3)*. On the other hand, the normal liver hepatocytes derive their blood supply primarily from the portal circulation. Thus, the administration of chemotherapy into the hepatic artery allows for selective drug delivery to the tumor, with relative sparing of normal hepatocytes.

The pharmacologic basis of intrahepatic therapy is well-defined. Certain drugs are extracted mostly by the liver during the first pass through the arterial circulation, which results in high local concentrations of the drug, with minimal systemic toxicity *(4)*. Because hepatic arterial blood flow has a high regional exchange rate (100–1500 mL/min), drugs with a high total body clearance and short plasma half-life are more useful for hepatic infusion. If a drug is not rapidly cleared, recirculation through the systemic circulation diminishes the advantage of hepatic arterial delivery. The area under the concentration vs time curve (AUC) is a function not only of drug clearance, but also of hepatic arterial flow.

Another rationale for HAI chemotherapy, especially for patients with metastatic CRC, is the concept of a stepwise pattern of metastatic progression *(5)*. According to this theory, hematogenous spread occurs first via the portal vein to the liver, then from the liver to the lungs, and then to other organs of the body. Therefore, aggressive treatment of metastases confined to the liver may prolong survival for some patients.

3. CHEMOTHERAPEUTIC AGENTS

Drugs with a steep dose–response curve are more useful when given by the intrahepatic route because small increases in the concentration of the drug result in a large improvement in response. Ensminger et al. *(6)* demonstrated that 94–99% 5-fluorodeoxyuridase (FUDR) is extracted during the first pass, compared to 19–55% of 5-fluorouracil (5-FU), which makes FUDR an ideal drug for HAI chemotherapy. Although, after injection of FUDR into either the hepatic artery or portal vein, mean liver concentrations of drug do not differ because of the route of injection, the mean tumor FUDR levels are 15-fold higher when the drug is injected via the hepatic artery. The pharmacological advantage of various chemotherapeutic agents used for HAI is summarized in Table 1.

4. ACCESS FOR HAI

4.1. Approach

Regional HAI can be done by using either hepatic arterial port or a percutaneously placed catheter connected to an external pump, or to a totally implantable pump. Early studies with percutaneously placed hepatic artery catheters produced high response rates, but clotting of the catheters and the hepatic artery, as well as bleeding, led physicians to abandon this method *(7)*. The development of a totally implantable pump

Table 1
Drugs for HAI

Drug	*Half-life (min)*	*Estimated increased exposure by HAI (-fold)*
Fluorouracil	10	5–10
5-Fluoro-2-deoxyuridine	<10	100–400
Bischlorethylnitrosourea	<5	6–7
Mitomycin C	<10	6–8
Cisplatin	20–30	4–7
Adriamycin (doxorubicin hydrochloride)	60	2

allowed long-term HAI with good patency of the catheter and the hepatic artery, and a low incidence of infection. One study compared three groups: surgical placement of hepatic artery catheter, percutaneous placement of hepatic artery catheter, and an operative implantable reservoir connected to the hepatic artery catheter. The reported ability of each technique to administer chemotherapy for the three groups was 31, 25, and 115 d, respectively *(5)*.

The goals of pump placement are to enable bilobar hepatic perfusion with chemotherapy, and to prevent administration of chemotherapy to the stomach or duodenum. Although this appears straightforward, the complication rate with pump placement may be unacceptably high in inexperienced hands *(8)*. Even with experienced surgeons, extrahepatic disease must be ruled out radiographically, with meticulous care. Celiac and superior mesenteric artery arteriograms should be done to identify arterial anatomy of the liver and vessels to the stomach, duodenum, and pancreas, preoperatively. Portal vein must be patent and portal lymph nodes should be biopsied intraoperatively, to rule out extrahepatic disease. The catheter is placed into the gastroduodenal artery, and not directly into the hepatic artery, which can lead to thrombosis. The catheter is secured with nonabsorbable ties. The arterial collaterals to stomach, duodenum, and pancreas are identified and ligated, and the liver perfusion, as well as absence of perfusion to other vital organs, is confirmed intraoperatively with fluorescein injection and Wood's lamp. A cholecystectomy is performed at the same time, to avoid drug-induced cholecystitis. Postoperative (PO) macroaggregated albumin scan should be performed through the side port of pump, to check for perfusion of the liver, and to ensure absence of extrahepatic perfusion *(9)*. Careful attention to these details is important to avoid unnecessary surgery and to minimize the risks of complications, including gastrointestinal (GI) ulceration and hemorrhage.

4.2. Complications

Early PO complications include arterial injury leading to hepatic artery thrombosis; incomplete perfusion of the entire liver caused by the lack of recognition of an accessory hepatic artery; misperfusion to the stomach, duodenum, or pancreas; and pump pocket hematoma *(10)*. Late complications tend to be more common, and include pump pocket infections, catheter thrombosis, and peptic ulceration. Review of data from Memorial Sloan-Kettering Cancer Center (MSKCC) over an 8-yr period showed relative lack of serious complications, in experienced hands. During this period, 303 infusion pumps were inserted for intrahepatic therapy. There were only two deaths. Arterial catheter

Table 2
Hepatic Arterial FUDR With Internal Pump: Responses

Investigator	*Ref.*	*No. Patients*	*Prior Chemotherapy (%)*	*Partial Response (%)*	*Decrease in CEA (%)*	*Median Survival (mo)*
Niederhuber	*(11)*	70	45	83	91	25
Balch	*(12)*	50	40	–	83	26
Kemeny, N.	*(13)*	41	43	42	51	12
Shepard	*(14)*	53	42	32	–	17
Cohen	*(15)*	50	36	51	–	–
Weiss	*(16)*	17	85	29	57	13
Schwartz	*(17)*	23	–	15	75	18
Johnson	*(18)*	40	–	47	–	12
Kemeny, M.	*(19)*	31	50	52	–	22
Lorenz	*(20)*	26	–	52	–	16

–, not stated.
CEA = carcinoembryonic antigen.

thrombosis occurred in 14 (4.7%) patients. Extrahepatic perfusion was seen in six (3%) patients. Incomplete perfusion occurred in five (1.7%), with the remaining complications occurring rarely, including gastric ulcers, hemorrhage, pneumonia, pocket infection, and faulty pump. Overall morbidity was seen in 34 of 303 patients (11.8%). Of the two patients who died, one died of myocardial infarction and the other died of progressive disease. The second patient underwent a laparotomy for resection of the colon primary and synchronous insertion of a pump. Although the operation was technically successful, without any significant complications, the extent of liver disease precluded a successful outcome. Patients who have more than 70% liver involvement may not benefit from surgical placement of hepatic artery pump for chemotherapy.

5. NONRANDOMIZED STUDIES OF HAI

5.1. Single-Agent Therapy

The development of a totally implantable infusional pump allowed for the safe administration of HAI chemotherapy in the outpatient setting. Early trials using an implantable pump and continuous FUDR therapy produced a median response rate of 45%, and a median survival of 17 mo (Table 2).

5.2. Combination Chemotherapy

Several phase II trials evaluating combination chemotherapy via HAI were conducted in the early 1990s. In a study at the University of California at San Francisco *(21)* (UCSF), 34 patients were treated with FUDR alternating with 5 FU, to take advantage of the different pharmacokinetics and toxicities of infusional FUDR and bolus 5 FU. FUDR was infused at a dose of 0.1 mg/kg/d for 7 d. Bolus 5 FU was given through the pump side port on d 15, 22, and 29 of each 5-wk cycle. There was a 50% response rate, with median survival exceeding 2 yr for previously untreated patients. Hepatobiliary toxicity was minimal with this regimen. However, progressive hepatic disease was the initial site of failure and cause of death in the majority of patients.

In a series of successive studies at MSKCC, Kemeny et al. *(22)* attempted modulation of FUDR by various agents, to improve response rate and decrease toxicity. In one

trial, six different regimens were explored. The FUDR dose ranged from 0.25 to 0.3 mg/kg/d for 14 d, along with 15–30 mg/m^2/d leucovorin (iv). Despite a 12% incidence of biliary cirrhosis, the median survival of 42 patients treated in the second phase was 24.2 mo. In a subsequent trial, Kemeny et al. *(23)* administered 0.3 mg/kg/d FUDR and 15 mg/m^2/d LV for 14 d with 20 mg dexamethasone (DEX) through the side port of the pump on day 1: 33 patients were treated on this regimen. Response rate was 78% and median survival was 24.8 mo. Strict dose-reduction protocol reduced the incidence of biliary cirrhosis to 3%. Liver was the initial site of failure in two-thirds of the patients.

6. RANDOMIZED STUDIES OF HAI VERSUS SYSTEMIC CHEMOTHERAPY

One of the first randomized trials was conducted at MSKCC by Kemeny et al. *(24)*. Prior to randomization, patients were stratified for extent of liver involvement by tumor and baseline lactic dehydrogenase (LDH), based on data showing them to be important prognostic indicators of survival. This prospective randomized trial compared HAI to systemic infusion of FUDR on a 14-d schedule. The dose of FUDR was 0.3 mg/kg/d in the HAI group and 0.125 mg/kg/d in the systemic group. The high dose given in the intrahepatic group was not tolerable by the systemic route. All patients underwent exploratory laparotomy, not only for pump placement, but to ensure the comparability of the two study groups, by accurately defining the extent of liver involvement, and assuring the absence of extrahepatic disease. The patients randomized to HAI had the hepatic artery catheter connected to the Infusaid pump (Shiley Infusaid, Norwood, MA). In patients randomized to systemic therapy, the hepatic artery catheter was connected to a subcutaneously implanted access port, and the pump was connected to an additional catheter placed in the cephalic vein. The study design allowed a crossover from systemic therapy to HAI by a minor surgical procedure, i.e., ligation of the systemic catheter, followed by connection of the pump with the hepatic artery catheter, in the event of tumor progression on systemic therapy. Of 178 patients referred, 12 refused randomization and four had an inadequate arterial blood supply; therefore, 162 were randomized. At laparotomy, 63 patients were excluded; 33 had extrahepatic disease, 25 had their tumor resected, four had no tumor, and one had an abdominal infection. Of the 99 evaluable patients, there were two complete responses (CRs) and 23 partial responses (PRs) (53%) in the group receiving HAI, and 10 partial responses (21%) in the systemic group (P = 0.001) (Table 3). Of the patients randomized to systemic therapy, 31 (60%) crossed over to HAI after tumor progression. Of these patients, 25% went on to a PR after the crossover, and 60% had a decrease in carcinoembryonic antigen levels. Toxicity differed between the two groups. In the HAI group, toxicity was predominantly hepatic and GI. An increase in hepatic enzymes and serum bilirubin (Bili) levels occurred in the intrahepatic group. In the systemic group, diarrhea occurred in 70% of the patients, with 9% requiring admission for iv hydration; mucositis occurred in 10% of patients.

The median survival for the HAI and systemic groups was 17 and 12 mo, respectively (P = 0.424). The interpretation of survival is difficult in this study, because 60% of the patients in the systemic group crossed over and received intrahepatic therapy after tumor progression on systemic therapy. Those who did not crossover usually had clotting of the hepatic arterial catheter, and had a median survival of only 8 mo, compared to 18 mo for those who crossed over to HAI (p = 0.04). An analysis

Table 3
MSKCC Study: Randomized HAI vs Systemic FUDR Infusion

	HAI (n = *48)*	*Systemic* (n = *51)*	P
Complete response	2	0	
Partial response	23 (52%)	10 (20%)	0.001
>50% decrease in CEA	29	13	
Extrahepatic metastases	27	19	0.09
Toxicity			
Ulcer	8	3	
Elevated enzymes	20 (42%)	12	
Bilirubin >3 mg/dL	9	2	
Diarrhea	1	36 (70%)	
Survival			
Total	17 mo	12 mo	0.424
Crossover		18 mo	
No crossover		8 mo	0.04

of baseline characteristics and the crossover and noncrossover groups revealed no significant differences.

A similar randomized study conducted by the North Carolina Oncology Group also used FUDR infusion in both HAI and systemic groups *(25).* Prior to randomization, the patients were stratified by extent of liver involvement, based on computed tomography (CT) scans, baseline bilirubin values, and performance status. The doses of FUDR were 0.2 and 0.075 mg/kg/d for 14 d in the HAI and systemic groups, respectively. These were the actual doses administered, because recalculation was done that took into account the residual volume in the pump. A total of 143 patients were entered, but only 117 were eligible. A 42% CR and PR rate was reported in the HAI group, and 10% in the systemic group ($P < 0.0001$). The median time to progression was 401 d in the HAI group and 201 d in the systemic group ($P = 0.0009$). The median survival was 503 and 484 d for the hepatic and systemic groups, respectively. Although a crossover design was not built into the study, 43% of the systemic group patients received intrahepatic therapy, possibly obscuring any difference in survival. Another factor that makes interpretation of survival difficult is that patients with metastases to hepatic lymph nodes were included in both study groups.

A National Cancer Institute study compared HAI to systemic infusion of FUDR in 64 patients *(26).* There was a significantly improved response rate for HAI, compared to the systemic therapy (62 vs 17%, respectively; $P < 0.003$). Interpretation of survival data is difficult because 11 (34%) patients of the HAI group never received chemotherapy, and 8% of the HAI group had positive portal lymph nodes. Despite these limitations, in the subset of patients without extrahepatic disease, the 2-yr survival was 47% in the HAI group vs 13% in the systemic group ($P = 0.03$).

Another small study conducted by the Mayo Clinic compared HAI FUDR (0.3 mg/kg/d for 14 d) to systemic bolus 5 FU (500 mg/m^2 iv for 5 d) *(27).* The trial only permitted entry of symptomatic patients, and did not allow a crossover to an alternative treatment; 69 patients were entered. Objective tumor response was observed in 48% of the patients receiving HAI FUDR, and in 21% of patients receiving iv 5 FU ($P = 0.02$). The time to hepatic progression was significantly longer in the HAI group (15.7 vs 6 mo; $P = 0.0001$). Despite the increased response rate and time to hepatic progression,

Table 4
Randomized Studies
of Intrahepatic vs Systemic Chemotherapy for Hepatic Metastases from CRC

Group (ref.)	No. patients	Response (%)			Survival (mo)		
		HAI	Sys	P	HAI	Sys	P
MSKCC *(24)*	162	52	20	0.001	18[a]	12	
NCOG *(25)*	143	42	10	0.0001	16.6	16	
NCI *(26)*	64	62	17	0.003	20	11	
Consortium *(31)*	43	58	38	–	–	–	
City of Hope *(30)*	41	56	0	–	–	–	
Mayo Clinic *(27)*	69	48	21	0.02	12.6	10.5	
French *(28)*	163	49	14	–	15	11	0.02
English *(29)*	100	50	0	0.001	13	6.3	0.03

–, not stated.
*Updated.

survival was similar in the two groups (12.6 mo for the HAI vs 10.5 mo for systemic therapy). Again, several factors must be considered regarding survival data. First, this was a small trial, and the power to detect survival advantage was very low. Second, of the 36 patients in the HAI group, five (14%) never received treatment, seven (19%) had extrahepatic disease, three (9%) had hepatic artery thrombosis, and two (6%) had pump malfunction. All of these patients were included in the survival analysis, even though 48% were not adequately treated or had extrahepatic disease. The investigators report that the survival of patients with extrahepatic disease is significantly shorter than those without extrahepatic disease ($P = 0.04$); therefore, inclusion of these patients in the HAI group will have a negative impact on survival. There is no comment in the report on the survival in the adequately treated patients.

In a large multicenter trial in France *(28)*, 163 patients were randomized either to hepatic arterial FUDR for 14 d or to systemic bolus 5 FU for 5 d every 4 wk. The groups had comparable clinical and laboratory characteristics, including percentage of liver involvement and baseline LDH levels. In patients with measurable disease, the response rate was 49% in the HAI group and 14% in the systemic group. The median time to hepatic progression was 15 mo for the former group and 6 mo for the latter group. Median survival was 14 vs 10 mo, favoring the HAI group. The 2-yr survival was 22% for the hepatic group and 10% for the systemic group ($P < 0.002$).

In a similar study done in England *(29)*, 100 patients were randomized to HAI FUDR vs systemic 5-FU. Patients were only treated if they were symptomatic. Quality of life and survival were significantly improved for the HAI group. Median survival was 405 d vs 198 d for the HAI and systemic groups, respectively ($P = 0.03$).

6.1. Summary of Randomized Studies

There are now eight randomized trials demonstrating a significantly high response rate for HAI chemotherapy compared to systemic therapy in patients with hepatic metastases from CRC (Table 4). In every study, the CR and PR rates were higher for HAI group. Whether this increase in response rate translates into increased survival remains controversial. Several factors complicate this issue. First, most of the trials contain relatively few patients, so that the power to observe differences in survival is low. Second, because of the early successes with intrahepatic infusion, some of these

Table 5
Randomized Study of HAI vs Systemic Chemotherapy

	Survival (%)							
	1 yr		*2 yr*		*<1 yr*		*<2 yr*	
Group (ref.)	*HAI*	*Sys*	*HAI*	*Sys*	*Crossover*	*No crossover*	*Crossover*	*No crossover*
MSKCC *(24)*	60	50	25	20	60	28	25	14
NCOG *(25)*	60	42	30	20	78	42	40	17
NCI[a] *(26)*	85	60	44	13				
France *(28)*	61	44	22	10				
Mean	66	49	30	18	69	35	37	15

[a]Excluding patients with hepatic lymph nodes.

studies allowed patients in the systemic arm to crossover to intrahepatic therapy after tumor progression on systemic therapy. This crossover may have negated any difference in survival between the two groups. The studies do demonstrate a survival advantage for the groups who receive subsequent HAI treatment, with a mean 1-yr survival of 69% for the patients who crossed over from systemic therapy to HAI vs 35% for the group who did not (Table 5).

7. ROLE OF ADJUVANT HAI

At the City of Hope, a randomized trial was conducted for patients who underwent resection of hepatic metastases from CRC *(30)*. A total of 91 patients were entered in three different groups. In group A, after resection of solitary metastases, patients were randomized either to no further treatment (AI) or to HAI (AII). In Group B, after a resection of multiple metastases, the patients were randomized to no further treatment (BII) or HAI (BI). In Group C, there was no resection, and patients were randomized to HAI (CI) or systemic 5-FU followed by HAI (CII). In the group with solitary liver metastasis, the time to failure was 9 mo in the resection-alone group (Group AI) and 31 mo in the resection + HAI (AII) ($P < 0.003$). In Group B, 30% of patients who had resection + HAI were alive at 5 yr vs 7% of those receiving resection alone. Thus, this study suggests a benefit for HAI in patients who have undergone resection of liver metastases.

An ongoing Eastern Cooperative Oncology Group study *(45)* randomized fully resected patients to observation vs a combination of HAI FUDR and infusional 5-FU. At 5 yr, actuarial survival is 63% for those treated with HAI vs 32% in the control group. At MSKCC, 15 resected patients were randomized to HAI + systemic vs systemic alone. At 2 yr, 85% are alive in the HAI group vs 69% in the systemic group ($P < 0.02$). The actuarial 5 yr survival is 60% and 45%, respectively *(46)*. Other pilot studies are exploring the role of HAI FUDR-based chemotherapy in conjunction with partial debulking of liver metastases, either via surgical resection or cryosurgery. Neoadjuvant HAI chemotherapy is also a consideration, but, like PO adjuvant HAI therapy, it must be considered investigational.

8. TOXICITY OF INTRAHEPATIC THERAPY

The most common problems with HAI are peptic ulceration and hepatic toxicity *(13,32)*. Severe ulcer disease results from the inadvertent perfusion of the stomach and duodenum via small collateral branches from the hepatic artery, and can be prevented

via careful dissection of these collaterals at the time of pump placement. However, even without radiologically visible perfusion of the stomach and duodenum, mild gastritis and duodenitis can occur. This toxicity can be reduced by careful dose reductions when any GI symptoms occur. Hepatobiliary toxicity is the most problematic toxicity seen with HAI chemotherapy. Although there is some evidence of hepatocellular necrosis and cholestasis on liver biopsies, most studies point to a combined ischemic and inflammatory effect on the bile ducts as the most important etiology of this toxicity. The bile ducts are particularly sensitive to HAI chemotherapy, because, like hepatic tumors, the bile ducts derive their blood supply almost exclusively from the hepatic artery. Pettavel et al. *(33)* prospectively studied 21 liver biopsies and four autopsy specimens of 13 patients, in whom biliary toxicity developed after HAI treatment with FUDR. The liver biopsies were characterized by portal or diffuse inflammatory changes that were predominantly mononuclear. Other changes included focal atrophy of hepatocytes and increased collagen formation. The autopsy specimens showed gross bile duct damage and intimal fibrous thickening of the small arteries, with narrowing or obstruction of the lumina.

Clinically, biliary toxicity is manifested as elevations of aspartate aminotransferase (AST), alkaline phosphatase, and Bili levels. Elevation of AST level is an early manifestation of toxicity; elevation of the alkaline phosphatase or bilirubin is evidence of more severe damage. In the early stages of toxicity, hepatic enzyme elevations will return to normal when the drug is withdrawn and the patient is given a rest. In more advanced cases, jaundice does not resolve.

In patients with severe toxicity, endoscopic retrograde cholangiopancreatography (ERCP) demonstrates lesions resembling primary sclerosing cholangitis. Because the ducts are sclerotic and nondilated, sonograms are usually unhelpful. In some patients, the strictures are more focal, usually worse at the bifurcation, and drainage procedures, either by ERCP or transhepatic cholangiography, may be helpful. Duct obstruction from metastases should first be excluded by CT scan of the liver.

Close monitoring of liver function tests is necessary to avoid biliary sclerosis. If the serum Bili level becomes elevated, no further treatment should be given until it returns to normal, and then only with a small test dose (0.05 mg/kg/d). In patients who cannot tolerate even a low dose for 2 wk, it may be possible to continue treatment by giving the FUDR infusion for 1 wk, rather than the usual 2 wk. At MSKCC, the serum AST level was found to be a useful laboratory test to monitor hepatic toxicity *(13)*. A review of the liver function tests obtained every 2 wk revealed that, in 23 of the original 45 patients, the AST level increased at the end of FUDR infusion (2 wk after treatment began), and then returned to normal, or almost normal, levels prior to the next dose (4 wk after treatment began). This pattern occurred in all patients who later developed severe hepatic toxicity (Bili >3 mg/dL). In some studies with excessive biliary sclerosis, liver function tests were only checked monthly. These investigators may have missed the 2-wk elevation, and therefore may not have reduced doses appropriately at the time of next treatment. At MSKCC, the dose of HAI chemotherapy is modified as outlined in Table 6. In older trials, cholecystitis occurred in up to 33% of patients receiving HAI chemotherapy. In more recent series, the gallbladder was removed at the time of catheter placement, to prevent this complication, and to avoid the confusion of these symptoms with other hepatic side effects of chemotherapy.

The side effects of systemic chemotherapy are almost never observed with HAI. Myelosuppression does not occur with intrahepatic FUDR. Although intrahepatic mitomycin C or carmustine (BCNU) may depress platelet counts, the absolute depression

Table 6
FUDR Dose Modification Schema

SGOT Reference Value:[a]	≤50 u/L	>50 u/L	
	SGOT at pump emptying or day of planned treatment (whichever is higher)		
			FUDR Dose
	0 to <3 × reference	0 to <2 × reference	100%
	3 to <4 × reference	2 to <3 × reference	80%
	4 to <5 × reference	3 to <4 × reference	50%
	≥5 × reference	≥4 × reference	Hold[b]
AP Reference Value:[a]	≤90 u/L	>90 u/L	
	AP at pump emptying or day of planned retreatment (whichever is higher)		
			FUDR Dose
	0 to <1.5 × reference	0 to <1.2 × reference	100%
	1.5 to <2 × reference	1.2 to <1.5 × reference	50%
	≥2.0 × reference	≥1.5 × reference	Hold[c]
Total Bili Reference Value:[a]	≤1.2 mg/dL	>1.2 mg/dL	
	Total Bili at pump emptying or day of planned retreatment (whichever is higher)		
			FUDR Dose
	0 to <1.5 × reference	0 to <1.2 × reference	100%
	1.5 to <2 × reference	1.2 to <1.5 × reference	50%
	≥2.0 × reference	≥1.5 × reference	Hold[d]

[a]Reference value is defined as the value obtained on the day the patient received the last FUDR dose. To determine if an FUDR dose modification is necessary, compare the reference value either to the value obtained on the day that the pump was emptied or to the value on the day of planned pump filling, whichever is higher.

Recommencing Treatment After Hold

[b]After treatment has been held because of elevated SGOT, chemotherapy cannot be restarted until the value has returned to within 4 × reference value (if reference ≤50 u/L) or within 3 × reference value (if reference >50 u/L). Then chemotherapy may be restarted using 50% of the last FUDR dose given.

[c]After treatment has been held because of elevated AP, chemotherapy cannot be restarted until the value has returned to within 1.5 × reference value (if reference ≤ 90 u/L) or within 1.2 × reference value (if reference >90 u/L). Then chemotherapy may be restarted, using 25% of the last FUDR dose given.

[d]After treatment has been held for elevated total Bili, chemotherapy cannot be restarted until value has returned to within 1.5 × reference value (if reference ≤1.2 mg/dL) or within 1.2 × reference value (if reference >1.2 mg/dL). Then chemotherapy may be restarted, using 25% of the last FUDR dose given.

Important: If the patient has experienced a marked elevation in Bili between the reference value and pump emptying (i.e., 2 × reference value, if reference value <1.2 mg/dL; 1.5 × reference value, if reference value >1.2 mg/dL), the patient must not receive chemotherapy on the date of the next planned pump filling, even if Bili has returned to normal. The pump should be filled with heparinized saline, and the patient's laboratory work should be reevaluated in 14 d. If, at that time, Bili is still not evaluated, and enzymes are within the range for treatment, the pump then may be filled with 25% FUDR of the last dose FUDR dose.

AP = Alkaline phosphatase; FUDR = floxuridine; SGOT = serum glutamic oxaloacetic transaminase; Total Bili = Total bilirubin.

and frequency of depression is less than with systemic administration. Nausea, vomiting, and diarrhea do not occur with HAI FUDR. If diarrhea does occur, shunting to the bowel should be suspected.

NEW APPROACHES TO DECREASE HEPATIC TOXICITY

New approaches to decrease hepatic toxicity induced by HAI FUDR are being studied. Because portal triad inflammation may lead to ischemia of the bile ducts, the HAI administration of Dex may decrease biliary toxicity. In patients with established hepatobiliary toxicity from HAI, Dex promotes resolution of liver function abnormalities. A prospective, double-blind randomized study of intrahepatic FUDR with DEX vs FUDR alone was conducted at MSKCC *(34)*, in order to determine whether the simultaneous administration of DEX with FUDR would prevent biliary toxicity, and thereby allow for administration of higher doses of chemotherapy. Although a significant increase in administered FUDR dose was documented, the response rate in 49 evaluable patients was 71% for the FUDR + DEX group vs 40% for FUDR alone. Survival also favored the FUDR + DEX group: 23 vs 15 mo. In addition, there was a trend toward decreased Bili elevation in patients receiving FUDR + DEX, compared to the group receiving FUDR alone (9 vs 30%; $P = 0.007$).

Use of circadian modification of hepatic intra-arterial FUDR infusion is another method to decrease hepatic toxicity. In a retrospective, nonrandomized study at the University of Minnesota *(35)*, a comparison of constant infusion vs circadian-modified HAI FUDR was conducted in 50 patients with CRC. The initial dose was 0.25–0.30 mg/kg/d for a 14-d infusion. The group at circadian modification received 68% of each daily dose between 3 and 9 PM, 2% between 3 and 9 AM, and 15% between each of the adjacent 6-hr periods. Over nine courses of treatment, the patients with circadian-modified infusion tolerated almost twice the daily dose of FUDR (0.79 vs 0.46 mg/kg/d). Circadian-modified infusion resulted in 46% of patients having no hepatic toxicity vs 16% of patients after constant FUDR infusion. Unfortunately, the authors do not present information on response rates achieved in both groups.

Another approach to decrease toxicity from HAI is to alternate drugs such as intra-arterial FUDR and intra-arterial 5-FU. Weekly intra-arterial bolus 5-FU has a similar activity to intra-arterial FUDR, and does not cause hepatobiliary toxicity; however, it frequently produces treatment-limiting systemic toxicity or arteritis. In a trial conducted by Stagg et al. *(21)*, FUDR by HAI was alternated with bolus intra-arterial 5-FU. No patient had treatment terminated because of drug toxicity. Metzger et al. *(36)*, using an infusion of 5-FU and mitomycin C, found that sclerosing cholangitis did not occur, but that mucositis and leukopenia did. Median survival was 18 mo, with a PR rate of 57%. Catheter complications occurred, which led to premature termination of treatment in one-third of patients.

10. METHODS TO INCREASE RESPONSE RATE

Because systemic combination chemotherapy regimens are more effective than single agents, the potential benefit of multidrug arterial therapy is being evaluated. In an early study using mitomycin C, BCNU, and FUDR, Cohen et al. *(37)* reported a 69% PR rate. In a randomized trial at MSKCC, comparing this three-drug regimen with FUDR alone, there was a slight increase in response rate and survival with the three-drug regimen *(38)*. In the 67 patients who entered this trial, all of whom had received prior systemic chemotherapy, the response rate was 45% for the three-drug regimen and

32% for FUDR alone. The median survival from the initiation of HAI therapy was 18.9 and 14.9 mo, respectively. It should be noted that the response rates in both arms are much higher than would be expected with the second systemic regimen. Thus, in addition to its role as a frontline treatment, HAI should also be considered in patients who have failed systemic therapy.

In another attempt to improve survival and response rate, a combination of HAI FUDR and LV was evaluated by Kemeny et al. *(39)*. This study was based on the success of systemic 5-FU/LV regimens, as well as on laboratory studies that suggested that LV may actually be a better modifier of FUDR than 5-FU. Sixty-four patients were treated at five dose levels. The overall response rate was 62%, but 15% of patients developed biliary sclerosis. Nevertheless, 75% of the patients were alive after 1 yr, 66% after 2 yr and 33% after 3 yr. FUDR + LV appears to have a high response rate in the treatment of hepatic metastases from CRC, but hepatic toxicity appears greater than previously reported with FUDR alone.

11. COMBINED HAI AND SYSTEMIC CHEMOTHERAPY

Extrahepatic disease develops in 40–70% of patients undergoing HAI. Such metastases can occur even when the patient is still responding in the liver, and, in many patients, it can result in death. Safi et al. *(40)* studied the ability of concomitant systemic chemotherapy to reduce the development of extrahepatic metastases in patients receiving HAI therapy. Ninety-five patients were randomized to either intra-arterial FUDR (0.02 mg/kg/d) or a combination of intra-arterial FUDR (0.21 mg/kg/d) and iv FUDR (0.09 mg/kg/d) given concurrently, for 14 of 28 d. The response rates were 60% for both arms of the study. However, the incidence of extrahepatic disease was significantly less in patients receiving the intra-arterial/iv treatment, compared with intra-arterial treatment alone (56 vs 79%; $P < 0.001$). No significant difference in survival was found between the two groups ($P = 0.08$). In the study conducted by Lorenz et al. *(41)*, combined HAI + iv therapy did not increase survival or decrease the development of extrahepatic disease (60% for HAI–systemic therapy vs 62% HAI alone).

A pilot study of HAI FUDR alternating with systemic 5-FU and LV was conducted at MSKCC *(42)*. Eight patients had liver metastases that were resected completely. FUDR was given at a dose of 0.25 mg/kg/d for 14 d. Systemic chemotherapy consisted of 200 mg/m^2 LV and 280 mg/m^2 5-FU, using a bolus dose of 5-FU for 5 d, with escalation of the 5-FU dose in separate patient cohorts. The maximally tolerated 5-FU dose was 325 mg/m^2. The median survival was 16 mo, with a PR rate of 56%. The level of hepatic toxicity was similar to that in previous studies done at MSKCC. One patient had documented biliary sclerosis. All eight patients treated with adjuvant therapy were alive without disease after a median follow-up of 23 mo.

12. FUTURE DIRECTIONS

During the past 20 yr, there has been no change in the survival for metastatic CRC. More than 2000 patients have been randomized to 5-FU + LV vs 5-FU alone. A meta-analysis of these studies demonstrated a median survival of 11 mo, and a 2-yr survival of less than 20% for both treatment groups *(43)*. Recently, new drugs have been developed for the treatment of CRC: irinotecan *(47)*, a Camptothecian derivative; Tomudex, a new thymidylate synthase inhibitor; and Oxaliplatin *(48)*, a new platinum compound. All of these drugs produced response rates similar to those obtained with 5-FU and LV. In many studies of these new agents, survival is similar, with 20% of

patients alive at 2 yr. Whether combinations of these agents will increase survival is yet to be tested.

In three recent studies of HAI using FUDR + LV, FUDR + DEX, and FUDR + LV and DEX, the median survivals were 23, 23, and 27 mo, respectively. The 2-yr survival rates in these studies were 61, 44, and 47%, respectively *(22,23,34)*.

Because of this apparent survival advantage of HAI chemotherapy, compared to systemic chemotherapy, a new randomized study was initiated by the Cancer and Leukemia Group B (CALGB) to ascertain whether these results can be reproduced. In that study, patients are first staged radiographically, to verify the absence of extrahepatic tumor. This staging includes a chest X-ray, CT scan of the abdomen and pelvis, and colonoscopy. Only patients with less than 70% of the liver involved by tumor are eligible. Patients are stratified according to the extent of liver involvement, prior chemotherapy, and presence or absence of synchronous disease. Patients are randomized either to HAI FUDR at a dose of 0.18 mg/kg/d and 10 mg/m^2/d LV for 14 d, with 20 mg DEX and 50,000 U heparin or to systemic chemotherapy consisting of 425 mg/m^2/d 5-FU following 20 mg/m^2/d LV, for five consecutive days. This cycle is repeated every 28 d. Crossover to the alternative treatment at the time of progression is strongly discouraged. The goal is 340 patients.

This CALGB study will address the following questions: Does HAI therapy improve survival in comparison to systemic chemotherapy? Is there a difference in the quality of life between the two treatments? Is there a difference in financial cost over the entire course of therapy? The lack of a crossover may provide a conclusive answer to these questions.

It has been shown that 24-h HAI infusion of 5-FU confers significant pharmacological advantage compared to iv infusions or intra-arterial bolus administration. Further evidence suggests that modulation of regional 5-FU administered with LV confers significant therapeutic advantage. Combining both approaches, a study was undertaken in which a fixed dose of 200 mg/m^2 LV iv over 2 hr was followed by a loading dose of 400 mg/m^2 5-FU over 15 min, followed by a 22-h infusion of 1.6 gm/m^2 5-FU, repeated on d 2 *(44)*. This cycle was repeated every 2 wk. Fifty-nine patients, with histologically proven metastases confined to the liver, received the therapy. The response rate of evaluable patients was 48%, with predicted median survival of 19 mo. The site of first progression was relatively balanced between hepatic and extrahepatic sites (42 vs 58%), respectively. The systemic toxicity was low, and so was the treatment complication rate. The therapeutic potential for this 5-FU-based HAI regimen vs systemic 5-FU–LV is being tested in a United Kingdom Medical Research Council (UK MRC)-sponsored phase III clinical trial in patients with disease confined to the liver. The conclusions from this trial will also help define the role of HAI chemotherapy in the management of unresectable hepatic metastatic disease.

13. CONCLUSION

There are several advantages to HAI. From a pharmacological standpoint, HAI is more effective than systemic therapy, because high drug levels are achieved at the sites of metastatic disease. Utilizing agents with high hepatic extraction results in minimal systemic toxicity. The high response rates obtained in trials of HAI FUDR in the treatment of CRC have not been matched by systemic trials. In eight randomized trials, the response rate was high with HAI, compared to systemic therapy. The time to hepatic progression was significantly longer in the HAI groups vs the systemic groups. None

of these studies was adequately designed to evaluate the issue of survival. The results of the randomized, phase III CALGB and UK MRC trials are expected to place the worth of HAI therapy in its proper perspective.

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