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PHASE I STUDIES

Dose-finding study of hepatic arterial infusion of irinotecan-based treatment in patients with advanced cancers metastatic to the liver

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Summary *Background* Liver metastases are associated with a poor prognosis. We investigated the use of hepatic arterial infusion (HAI) of irinotecan combination therapy in patients with liver metastases. *Patients and methods* Patients with histologically confirmed advanced cancer with liver metastases that was refractory to standard therapy were eligible. A standard "3+3" phase I study design was used to determine the dose-limiting toxicity (DLT) and the maximum tolerated dose (MTD). Three cohorts were evaluated: HAI of irinotecan with systemic intravenous (IV) (a) bevacizumab, (b) oxaliplatin and bevacizumab, or (c) bevacizumab and cetuximab. *Results* From October 2009 through December 2013, 98 patients with various tumor types were enrolled (median age, 62 years, range, 34-85; and median number of prior therapies, 4, range, 1–11). In cohorts A and C, dose escalation continued until the highest dose level—considered the MTD—was reached. In cohort B, dose escalation continued until dose level 3, and dose level 2 was considered the MTD. Rates of grade 3/4 adverse events were as follows: diarrhea, 8 %; fatigue, 4 %; neutropenia, 4 %; thrombocytopenia, 2 %; and skin rash, 2 %. Seventy-seven patients were evaluable for response. Partial response was noted in 5 (6.5 %) patients (neuroendocrine cancer, n=2; CRC, n=2; NSCLC, n=1); and stable disease≥ 6 months in 17 (22.1 %) patients (CRC, n=13; breast, n=1; neuroendocrine, n=1; NSCLC, n=1; pancreatic, n=1). *Conclusions* HAI irinotecan in combination with bevacizumab; oxaliplatin plus bevacizumab; or cetuximab plus bevacizumab was safe and may be a treatment option for selected patients with advanced cancer and liver involvement.

Keywords Liver metastasis · Phase I trial · Hepatic arterial infusion · UGT1A

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Introduction

The liver is a common metastatic site for various solid tumors, including gastrointestinal malignancies, lung carcinoma, breast carcinoma, ovarian carcinoma, and melanoma. The overall prognosis of patients with metastatic cancer to the liver is dismal, with a median survival duration of 7.5 months when treated on phase I clinical trials [1]. The treatment options for metastatic liver disease include systemic therapy, surgical resection, and—for selected patients–regional therapy [2].

Hepatic arterial infusion (HAI) of chemotherapy is a regional therapy that results in preferential flow distribution to and higher drug concentration in metastatic liver lesions, along with reduced systemic exposure and side effects [3, 4]. Various agents, including platinum agents, taxanes, 5-fluorouracil, leucovorin, interferon, and interleukin-2, have been

used in HAI protocols [5–14]. In some randomized trials, the use of HAI treatment resulted in higher rates of response, progression-free survival, and overall survival (OS) compared to systemic therapy [15, 16]. However, an OS benefit of HAI has not been confirmed in all trials [17, 18].

We have previously investigated the use of HAI oxaliplatin, cisplatin, or abraxane in combination regimens [19–23], which demonstrated antitumor activity in selected patients with advanced cancer and predominant liver metastasis. Irinotecan is a water-soluble derivative of camptothecin that exerts potent anti-cancer activity by inhibiting the nuclear enzyme topoisomerase I. The activity of irinotecan is due to the parent compound and the active metabolite 7-ethyl-10-hydroxycamptothecin (SN-38). Irinotecan is approved by the Food and Drug Administration (FDA) for the treatment of metastatic colorectal carcinoma, and it is used off-label for the treatment of other tumor types, including pancreatic, ovarian, lung, and gastric cancer.

The safety and the maximum tolerated dose (MTD) of HAI irinotecan as a single agent has been studied in various phase 1 trials using either small fractionated daily doses as a continuous infusion over 5 days or a large single dose over 30 min every 3–4 weeks [24, 25]. Subsequently, phase II trials have confirmed the clinical benefit associated with the use of this drug in patients with CRC and liver metastases [26, 27]. In this setting, the addition of oxaliplatin to the systemic administration of irinotecan increased the response rate and time to tumor progression, improved tumor-related symptoms, and significantly increased OS [28]. Furthermore, adding irinotecan to cetuximab and bevacizumab improved the response rate, time to tumor progression, and OS in metastatic CRC [29]. In addition, bevacizumab significantly improved OS, time to tumor progression, and response rate when added to an irinotecan, 5-fluorouracil, and leucovorin regimen [30]. Therefore, we conducted a phase I study of HAI of irinotecan combined with systemic intravenous (IV) bevacizumab, oxaliplatin and bevacizumab, or bevacizumab and cetuximab in patients with advanced cancers with liver metastases. The objectives of this study were to determine the MTDs and dose-limiting toxicities (DLTs) and to assess the anti-tumor activity of these combinations, if any.

Methods

Patients

Study participants were treated in the phase I clinical trials program at The University of Texas MD Anderson Cancer Center. Patients enrolled in this trial had histologically confirmed metastatic advanced cancers with liver involvement that were refractory to standard therapy or for which no available standard therapy improved survival by at least 3 months. Inclusion criteria included adequate renal (serum creatinine≤ 2.5 times the upper limit of normal [ULN]), liver (total bilirubin≤3 mg/dL and ALT≤5X ULN), and bone marrow (absolute neutrophil count≥1000 cells/μL and platelet count≥100, 000 cells/μL) function. Additionally, patients had been off previous chemotherapy or radiotherapy for at least 3 weeks.

Exclusion criteria included pregnancy or lactation; abdominal fistula; gastrointestinal perforation or intra-abdominal abscess within 28 days; invasive procedures including major surgical procedures within 28 days or anticipation of need for such procedures during the study; bleeding diathesis; active gastric or duodenal ulcer; hypersensitivity to any drug in the regimen; heparin-induced thrombocytopenia; or uncontrolled systemic vascular hypertension. Patients with colorectal cancer and *KRAS* mutation were excluded from the cetuximab arm.

All participants signed informed consent forms fully disclosing the investigational nature of the trial. The protocol was approved by and conducted according to the guidelines of the MD Anderson Cancer Center Institutional Review Board.

Treatment

Enrolled patients received a consultation from the interventional radiology service, and a hepatic intra-arterial catheter was placed by an interventional radiologist using the femoral approach. A 5-French angiographic catheter was utilized to select the celiac and/or superior mesenteric artery, and a coaxial 3-French micro-catheter was advanced into the desired hepatic artery. Following the injection of 5 mCi of technetium ^{99m}Tc albumin aggregated (99mTc-MAA) particles through the HAI catheter (used to stimulate the distribution of the chemotherapeutic agent), a nuclear medicine flow study was performed to identify any evidence of extra-hepatic flow that could increase the risk of gastrointestinal complications. The catheter was removed at the end of the irinotecan infusion.

This was a standard "3+3" study designed to determine the DLT and the MTD. Patients were enrolled in a treatment cohort on the basis of their prior response to therapy, prior adverse events experienced, preference, and physician's choice. The dose escalation schedules for the three cohorts are summarized in Table 1. Cohort A consisted of HAI irinotecan continuous infusion ranging from 35 to 75 mg/m^2 daily, on days 1 to 3 and systemic IV bevacizumab 10 mg/kg on days 1 and 15 (60–90 min). Cohort B consisted of HAI irinotecan continuous infusion 35 to 75 mg/m^2 continuous infusion on days 1 to 3, IV oxaliplatin ranging from 60 to 100 mg/m^2 on days 1, and 15 (over 2 h); and IV bevacizumab 10 mg/kg on days 1 and 15 (60–90 min). Arm C consisted of HAI irinotecan continuous infusion 35 to 75 mg/m^2 continuous infusion on days 1 to 3, cetuximab 500 mg/kg on days 1 and 15 (over 2 h), and IV bevacizumab 10 mg/kg on days 1 and 15 (60–90 min). The treatment cycles were repeated every

Table 1 Dose escalation schedules

Cohort A	Irinotecan, mg/m^2 daily, HAI, q4 weeks	Bevacizumab, mg/kg, IV, q2 weeks		No. of patients treated	No. of patients who completed cycle 1
1	35	10		6	6
2	45	10		3	3
3	60	10		4	4
4	75	10		6	6
Expansion	75	10		18	17[a]
Cohort B	Irinotecan, mg/m^2 daily, HAI, q4 weeks	Bevacizumab, mg/kg, IV, q2 weeks	Oxaliplatin, mg/m^2, IV, q2 weeks	No. of patients treated	No. of patients who completed cycle 1
1	35	10	60	6	6
2	45	10	60	6	6
3	45	10	80	4	2[b]
Expansion	45	10	60	19	16
Cohort C	Irinotecan, mg/m^2 daily, HAI, q4 weeks	Bevacizumab, mg/kg, IV, q2 weeks	Cetuximab, mg/m^2, IV, q2 weeks	No. of patients treated	No. of patients who completed cycle 1
1	35	10	500	6	5
2	45	10	500	3	3
3	60	10	500	6	6
4	75	10	500	3	3
Expansion	75	10	500	8	8

Abbreviations: *HAI* hepatic arterial infusion, *IV* intravenous

[a] One patient withdrew consent before completing cycle 1

[b] Two patients did not complete cycle 1 because of toxicity

4 weeks in all cohorts until unacceptable toxicity or disease progression occurred. Patients underwent physical examination, hematology and chemistry laboratory studies, and imaging studies at baseline and after every two cycles.

Endpoints and statistical considerations

All treated patients were included in the toxicity analysis using the National Cancer Institute Common Toxicity Criteria, version 3.0. DLT was assessed during the first cycle and was defined as any grade 3 or 4 non-hematologic toxicity (except nausea/vomiting or electrolyte imbalances responsive to appropriate regimens, or alopecia); grade 4 hematologic toxicity lasting ≥3 weeks or associated with bleeding and/or sepsis; grade 4 nausea or vomiting lasting>5 days despite antinausea regimens; or any other severe or life-threatening complication [31].

Best response was assessed every two cycles by an MD Anderson radiologist and verified by a measurement team within our department using Response Evaluation Criteria in Solid Tumors (RECIST) [32]. OS was measured from the date of treatment on protocol until death from any cause or last follow-up. Time to treatment failure (TTF) was measured from the date of treatment on protocol until patients went off-study owing to toxicity, disease progression, or death.

Results

Patient demographics

From October 2009 through December 2013, 98 patients were enrolled. Patients' characteristics per each therapeutic cohort are listed in Table 2. The median age of patients at enrollment was 62 years (range, 34-85 years). Fifty-two percent were men and 48 % women. Overall, 84 % of patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and 77 % of patients had CRC. All patients had predominant liver involvement. Liver was the only site of metastasis in 8 (8 %) patients (CRC, n=6; cholangiocarcinoma, n=1; and neuroendocrine cancer, n=1). Sixty percent of patients had >2 metastatic sites. The median number of prior therapies was 4 (range, 1–11), and the median time from diagnosis to the first treatment cycle on study was 3 years. Prior therapy included irinotecan, bevacizumab, oxaliplatin, and cetuximab in 80 % (n=78), 81 % (n=79), 82 % (n=80), and 44 % (n=43) of patients, respectively. Of 98 patients, 77 % (n=76) had known tumor *KRAS* mutational status (43 % [n=34] positive and 57 % [n=42] negative).

Dose escalation and toxicity

In total, 418 cycles were administered, with a median of four cycles (range, 1–18) per patient. All patients were evaluable

Table 2 Patient demographics

Patients' Characteristics	Cohort A (*n*=37)	Cohort B (*n*=35)	Cohort C (*n*=26)	Total (*n*=98)
Sex				
Men (%)	15 (41)	22 (63)	14 (54)	51 (52)
Women (%)	22 (59)	13 (37)	12 (46)	47 (48)
Race				
White	22 (59)	24 (69)	16 (62)	62 (63)
Black	8 (22)	9 (26)	7 (27)	24 (24)
Other	7 (19)	2 (5)	3 (11)	12 (13)
Age, years				
Median	62	61	59	62
Range	41–85	44–80	34–77	34–85
No. of prior therapies				
Median	4	4	5	4
Range	1–11	1–10	1–11	1–11
LDH				
≤ULN	10 (27)	3 (9)	2 (8)	15 (15)
>ULN	27 (73)	32 (91)	24 (92)	83 (85)
Albumin				
≥ULN	30 (81)	25 (71)	18 (69)	73 (74)
<ULN	7 (19)	10 (29)	8 (31)	25 (26)
Number of metastatic sites				
≤2	12 (32)	17 (49)	10 (38)	39 (40)
>2	25 (68)	18 (51)	16 (62)	59 (60)
Median time from diagnosis to first cycle, years	2.5	2	3	3
Performance status, >1 (%)	6 (16)	5 (14)	5 (19)	16 (16)
KRAS mutation status				
Positive	19 (51)	12 (34)	3 (12)	34 (35)
Negative	12 (32)	10 (29)	20 (77)	42 (43)
Unknown	6 (17)	13 (37)	3 (11)	22 (22)
Tumor type (%)				
CRC	29 (78)	22 (61)	24 (92)	75 (77)
Others	8 (22)	13 (39)	2 (8)	23 (23)
Prior Therapies				
Irinotecan	29	27	22	78
Bevacizumab	29	27	23	79
Oxaliplatin	30	26	24	80
Cetuximab	11	10	22	43

Abbreviations: *ULN* upper limits of normal, *CRC* colorectal cancer

for toxicity assessment. The placement of the hepatic arterial catheter and the delivery of chemotherapy via HAI were not associated with any significant complications. The numbers of patients treated in each cohort and at each dose level are summarized in Table 1. The most common adverse event was prolonged diarrhea (up to 10 days), which resulted in a protocol amendment after 15 patients were treated using the 3-day regimen (cohort A, *n*=6; cohort B, *n*=6; and cohort C, *n*=3). With this amendment, the HAI irinotecan infusion was decreased from 3 days to 2 days in order to increase patient safety and improve the feasibility of administration of irinotecan (avoiding delay of subsequent cycles).

In cohort A, no DLT was noted at dose levels 1 to 3. At dose level 4, one of the first three patients experienced grade 3 nausea, vomiting, and fatigue; three additional patients were enrolled at dose level 4, and none of them experienced a DLT. Therefore, 18 patients were enrolled in the expansion phase at dose level 4 (irinotecan at 75 mg/m^2 and bevacizumab at 10 mg/kg), and none experienced a DLT.

In cohort B, no DLT was noted at dose levels 1 and 2. However, at dose level 3, one of three patients experienced grade 3 diarrhea, as did the fourth patient subsequently enrolled. Therefore, dose level 2 was considered the MTD. Subsequently, 19 patients were enrolled in the expansion phase at dose level 2 (irinotecan at 45 mg/m^2, bevacizumab at 10 mg/kg, and oxaliplatin at 60 mg/m^2), and none developed a DLT.

In cohort C, one of the first three patients developed a DLT (grade 3 diarrhea) at dose level 1. Three additional patients treated at dose level 1 did not experience a DLT. Dose escalation continued without a DLT to dose level 4. Eight patients were enrolled in the expansion phase at dose level 4 (irinotecan at 75 mg/m^2, bevacizumab at 10 mg/kg, and cetuximab at 500 mg/m^2), and none developed a DLT.

Adverse events that were at least possibly related to treatment are summarized in Table 3. The most common adverse events overall were diarrhea, fatigue, nausea, and skin rash. Diarrhea and fatigue were the most common adverse events in all cohorts. Severe adverse events included grade 3 diarrhea (8 %), grade 3 fatigue (4 %), grade 3/4 neutropenia (4 %), grade 3 thrombocytopenia (2 %), and grade 3 skin rash (2 %).

Table 3 Adverse events reported in at least 5 % of patients (All Arms)

Adverse event	G1 (%)	G2 (%)	G3 (%)	G4 (%)	Total (%)
Non-Hematologic					
Diarrhea	35 (36)	12 (12)	8 (8)		55 (56)
Fatigue	26 (27)	13 (13)	4 (4)		43 (44)
Nausea	23 (23)	3 (3)	1 (1)		27 (28)
Skin rash	14 (14)	5 (5)	2 (2)		21 (21)
Anorexia	11 (11)	7 (7)	1 (1)		19 (19)
Neuropathy	17 (17)				17 (17)
Vomiting	13 (13)	2 (2)	1 (1)		16 (16)
Pain	9 (9)				9 (9)
Hypertension	7 (7)	1 (1)			8 (8)
Hypokalemia	6 (6)				6 (6)
Constipation	5 (5)	1 (1)			6 (6)
Hematologic					
Neutropenia	5 (5)	2 (2)	3 (3)	1 (1)	11 (11)
Anemia	9 (9)	2 (2)			11 (11)
Thrombocytopenia	6 (6)		2 (2)		8 (8)

The total numbers of cycles that were administered at the highest dose level/expansion phase were as follows: in cohort A, 24 patients received a total of 93 cycles (median, 2.5 cycles; range, 1–18); in cohort B, 25 patients received a total of 108 cycles (median, 4 cycles; range, 1–15); and in cohort C, 11 patients received a total of 61 cycles (median, 4 cycles; range, 1–12).

The placement of the hepatic arterial catheter and the delivery of chemotherapy via HAI were not associated with any significant complications. In situations when anatomic variants were identified, they were either addressed by embolizing appropriate variant branches to skeletonize the hepatic circulation or catheters were placed into individual variant branches to avoid non-target infusion of chemotherapy to the gastrointestinal tract. Nuclear medicine flow studies were routinely performed on the initial HAI session to ascertain the presence of un-anticipated extrahepatic flow to the gastrointestinal tract that was not visible on angiography. This was accomplished by injecting 5 mCi of technetium 99mTc albumin aggregated (99mTc-MAA) particles through the HAI catheter (used to stimulate the distribution of the chemotherapeutic agent). There was no special attention to avoiding the cystic artery regarding catheter tip position and thus chemotherapeutic infusion of the cystic artery was likely present in the majority of patients.

Antitumor activity

Overall, all patients (n=98) were included in the TTF and OS analysis. However, only 77 (78 %) patients were evaluable for response assessment per RECIST. The remaining 21 (22 %) patients were not evaluable for the following reasons: rapid disease progression, transfer to hospice care, or death (n=13); consent withdrawal (n=6); severe neutropenia/sepsis (n=1); and discontinuation of the study therapy for >2 months because of palliative radiation therapy (n=1). Table 4 summarizes response by tumor type and cohort. Overall, partial response (PR) was noted in 6.5 % (n=5) and stable disease (SD) lasting at least 6 months was noted in 22.1 % (n=17) of patients (Fig. 1 and Table 4).

At the time of this analysis, all patients were off-study and only one patient was still alive. Overall, the median TTF and

Table 4 Clinical outcomes by tumor type and treatment cohort

Tumor Type	No. of pts	No. of evaluated pts per RECIST	PR (%)	SD≥6, months (%)	Median TTF, months (All patients)	Median survival, months (All patients)
Cohort A						
CRC	29	22		6(27)	3.67	6.67
Pancreatic	2	1			0.95	1.60
Hepatocellular	2	1			2.38	4.27
Bladder	1	1			4.83	6.37
Breast	1	1		1 (100)	6.60	9.10
Anal squamous cell	1	1			2.77	11.97
GIST	1	1			1.87	9.33
Total	37	28		7 (25)	3.43	6.37
Cohort B						
CRC	23	18		3 (18)	2.47	4.9
Neuroendocrine	3	3	2 (67)	1 (33)	7.65	9.33
NSCLC	3	2	1 (50)	1 (50)	6.30	7.17
Pancreatic	2	2		1 (50)	9.08	12.37
Cholangiocarcinoma	1	1			5.57	16.57
Adenocarcinoma	1				0.70	0.73
Gastric carcinoma, Signet ring	1				0.93	3.10
Esophageal	1				1.40	3.53
Total	35	26	3 (12)	6 (23)	2.73	5.9
Cohort C						
CRC	24	22	2 (9)	4(18)	4.62	6.87
Fallopian tube	1				1.27	1.30
Hepatocellular	1	1			5.30	6.57
Total	26	23	2(9)	4 (17)	4.62	6.45
Total (all cohorts)	98	77	5 (6.5)	17 (22)	3.72	6.35

Abbreviations: *CRC* colorectal carcinoma, *GIST* gastrointestinal stromal tumor, *NSCLC* non-small cell lung cancer

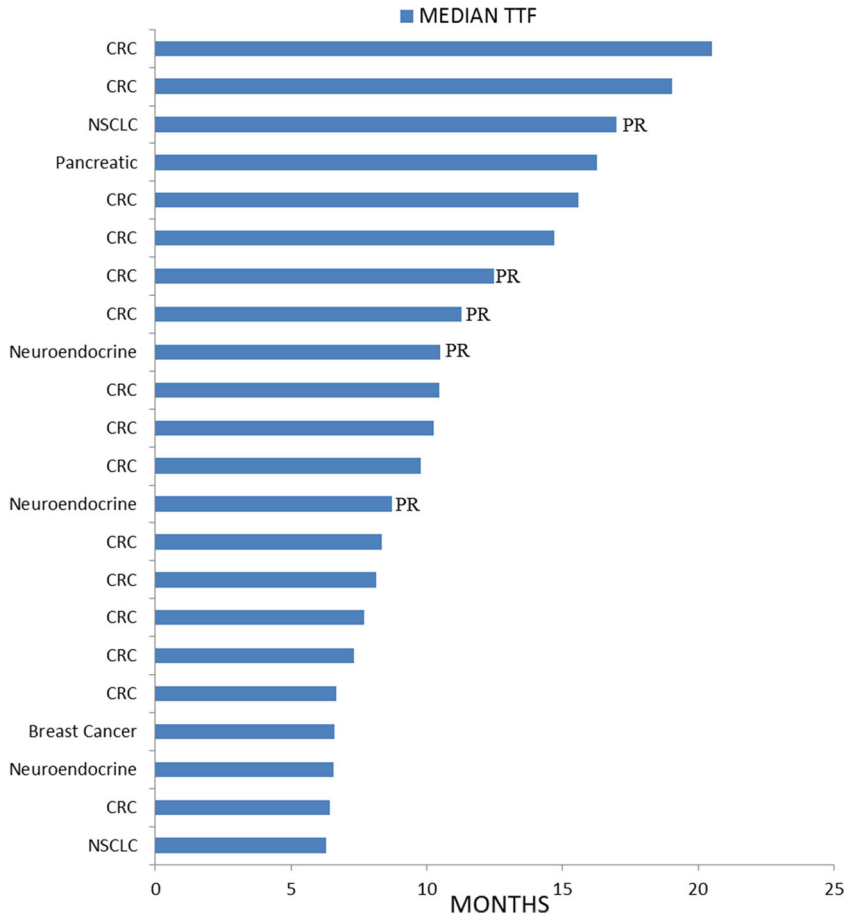

Fig 1 Patients with Clinical Benefit* by Tumor Type. *CRC* colorectal carcinoma, *PR* partial response. *Clinical benefit= stable disease for more than 6 months (n=17) plus partial response (n=5)

OS were 3.7 months (range, 0.2–19.0 months) and 6.3 months (range, 0.2–27.2 months), respectively. The median TTF durations were 3.4, 2.7, and 4.6 months in cohorts A, B, and C, respectively.

Clinical response with TTF lasting longer than 12 months was observed in seven patients. Details on their clinical and treatment characteristics are summarized in Table 5. Three patients withdrew consent while clinical benefit was still ongoing because of diarrhea. The median number of metastatic sites in these seven patients was two (range, 1-4), and the median number of prior therapies was six (range, 4–8). Of the seven patients, five had CRC that was relapsed/refractory to irinotecan, oxaliplatin, bevacizumab, and cetuximab.

Discussion

Our study demonstrated that in patients with various relapsed/refractory solid tumors and liver metastases the combination of HAI irinotecan with systemic bevacizumab, bevacizumab and oxaliplatin, or bevacizumab and cetuximab was safe. As expected, the most common adverse events were diarrhea and fatigue. Diarrhea was the most clinically challenging event, prompting a protocol amendment to decrease the infusion period of HAI irinotecan from 3 days to 2 days. Although diarrhea remained a common adverse event after the amendment, the 2-day irinotecan infusion was relatively well tolerated. Overall, diarrhea was seen in 56 % of patients (grade 3, 8 %); this rate is in line with that reported in a previous study of HAI irinotecan in which diarrhea (mostly grade 2) was reported in 41 % of patients with CRC who received HAI irinotecan as a single agent at 200 mg/m^2 once every 3 weeks [27]. In another study, diarrhea was reported in 84 % of patients (grade 3–4, 28 %) with CRC and liver metastases who were treated with single-agent HAI irinotecan in a dose-escalating trial at a daily dose of up to 20 mg/m^2 for 5 days [26].

The overall reported experience does suggest, however, that diarrhea is less frequent and severe with HAI irinotecan regimens (41–56 %; grade 3, 8 %) than with IV irinotecan regimens (60–80 %; grade 3–4, up to 27 %) [33–36].

The incidence of neutropenia in our study was 11 % (grade 3–4, 4 %), which is in line with previously reported data showing that myelosuppression was not a major issue with HAI irinotecan, and no grade 3–4 neutropenia was reported [26]. Again, the rates of neutropenia with HAI irinotecan are much lower than would be predicted, given the high incidence

Table 5 Patients with time-to-treatment failure longer than 12 months

Tumor Type	Sex	Time from diagnosis to initiation of treatment, months	Cohort	Dose Level	# of Metastatic sites	Prior Therapy regimen	RECIST	TTF	OS
CRC	M	23.5	C	1	2	1- FOLFOX+Bevacizumab 2- 5-FU+LV+Bevacizumab 3- Cetuximab+Irinotecan 4- Capecitabine 5- Irinotecan	PR	12.5	14.3
CRC	M	20.5	C	4	1	1- FOLFOX 2- FOLFOX+bevacizumab 3- 5-FU+Bevacizumab 4- Cetuximab+Irinotecan 5- Capcitabine 6- Capcitabine+Oxaliplatin +Bevacizumab	PR	14.7	14.7
CRC	M	49	B	1	2	1- FOLFOX+Bevacizumab 2- FOLFIRI+Cetuximab 3- FOLFOX+Cetuximab 4- FOLFOX+Vectibix 5- FOLFIRI+Bevacizumab 6- FOLFIRI+Vectibix 7- 5-FU+Vincristine+Mitomycin +Cetuximab 8- 5-FU+Leucovorin+Carboplatinum +Cetuximab	SD	15.6	21.5
CRC	M	53	A	4	2	1- XELOX 2- FOLFIRI+Bevacizumab 3- FOLFOX; 5-FU+Bevacizumab 4- Cetuximab 5- AMG 337	SD	19.0	25.8
CRC	M	51	C	4	3	1- FOLFIRI+Bevacizumab 2- Capcitabine+Irinotecan 3- Cetuximab+Irinotecan 4- Cetuximab 5- Capcitabine 6- Irinotecan+Oxaliplatin	SD	20.5	23
Pancreatic	F	19.5	B	1	2	1- Gemcitabine+Erlotinib 2- Gemcitabine+Capecitabine 3- Gemcitabine+Capecitabine+Erlotinib 4- Erlotinib 5- Gemcitatine+Carboplatin 6- Gemcitabine+Docetaxel	SD	16.3	19.8
NSCLC[a]	F	77	B	2	4	1- Cisplatin+Gemcitabine 2- Premetrexed+Docetaxel 3- Vinorelbine+Mitomycin+Bevacizumab 4- Bevacizumab 5- Erlotinib 6- Docetaxel 7- Vinorelbine 8- Trientine+Carboplatin	PR	17.9	17.9

Abbreviations: *CRC* colorectal, *NSCLC* non-small cell lung cancer

[a] Patient withdrew consent

of myelosuppression reported with systemic irinotecan infusion (overall, 60 to 90 %; grade 3–4, 20–30 %) [34–36].

Over the last two decades, numerous investigations had been conducted to establish a predictive marker of irinotecan toxicity, but despite the wealth of knowledge about the metabolism of irinotecan, including esterase-, UGT-, CYP3A-, and β-glucuronidase-mediated biotransformation [37, 38], inter-patient variability in irinotecan toxicity is commonly seen and an optimal dose has yet to be established [39–43]. The clinical implication of germline isoforms of UGT1A has not been determined, and testing is not routinely performed. At relatively high irinotecan dose levels (>250 mg/m^2), patients homozygous for the UGT1A1*28 may experience a greater risk of clinically important neutropenia, but at lower doses (100–125 mg/m^2), the negative impact of UGT1A1*28 has less clinical relevance [44]. Recently, a novel prediction system using a statistical pattern based on UGT1A genotypes, age, and sex was developed; despite the difference in treatment regimens between the training and validation patients, its predictive performance was high [45]. Others investigators explored the correlation between biliary index (irinotecan total x SN-38 total/SN-38G) and toxicity in patients treated with HAI irinotecan, and unfortunately, no correlation was seen [24].

In contrast to prior reported data for HAI irinotecan combined with other chemotherapeutic agents, severe hyperbilirubinemia was not noted in our patients. Grade 3–4 hyperbilirubinemia (usually associated with abdominal pain) was previously reported in patients treated with HAI oxaliplatin (up to 10 %), fluorodeoxyuridine (up to 8.5 %), and nab-paclitaxel (3.1 %) [9, 46–52]. In our study, one patient had grade 1 hyperbilirubinemia, which was not associated with epigastric or abdominal pain. In contrast, two previous studies with HAI irinotecan reported abdominal pain with no significant hyperbilirubinemia [26, 27]. Whether the phenomenon of "severe transient hyperbilirubinemia" seen in HAI of chemotherapeutic agents is related to pharmacological characteristics of the chemotherapeutic agents or to other mechanisms is unknown [53].

Our study demonstrated a clinical benefit (PR and SD≥ 6 months) in 28.5 % of patients. In addition, prolonged TTF (up to 20 months) was noted in selected patients with CRC, pancreatic cancer, and non-small cell lung cancer (Table 5). These results suggest that HAI irinotecan in combination with IV bevacizumab, oxaliplatin plus bevacizumab, or cetuximab plus bevacizumab is a good treatment option for selected patients, especially patients with high disease burden in the liver.

The rationale for choosing a 3-day continuous infusion of irinotecan was based on our intention to have the highest tolerable peak effect of the drug level possible. The same dose of irinotecan was administered as in the 5-day infusion regimen. The 3-day period was also chosen because it was easier for patients compared to the 5-day infusion period. We chose not to investigate the continuous infusion of 5-Fluorouracil (ci5FU) in this regimen, because our aim was to explore unique combinations since the ci5FU had already been explored in our HAI therapies with oxaliplatin, including the combination of HAI ci5FU and HAI oxaliplatin. We observed that HAI ci5FU was not associated with more treatment benefit than the ci5FU and it caused patient inconvenience.

The limitations of this HAI treatment include (1) the requirement for specialized centers with experienced interventional radiologists and other health care providers, (2) the high cost associated with the placement of an HAI catheter, and (3) the need for patient hospitalization and monitoring. The treatment is arduous, requiring that patients remained in a supine position for 48 h (recommended HAI irinotecan infusion period) to prevent catheter misplacement. As expected, the clinical outcomes of these HAI irinotecan regimens were poorer than those of HAI oxaliplatin regimens, as previously shown [19–23]. However, keeping in mind that some patients with CRC cannot tolerate oxaliplatin, HAI irinotecan combination therapy is a reasonable alternative in patients with CRC.

In conclusion, HAI irinotecan in combination with IV bevacizumab, oxaliplatin plus bevacizumab, or cetuximab plus bevacizumab is safe and may be a treatment option for selected patients with neuroendocrine, CRC, NSCLC, breast, or pancreatic cancer with extensive liver involvement for whom standard treatment options have been exhausted and who are expected to benefit from HAI irinotecan-containing therapy. A benefit from irinotecan by HAI as part of a multidrug regimen for patients with predominant liver metastases from CRC and neuro-endocrine tumors needs to be established in a randomized study before recommending it as a treatment option.

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