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ORIGINAL ARTICLE

Transient severe hyperbilirubinemia after hepatic arterial infusion of oxaliplatin in patients with liver metastases

Sean S. Garcia · Johnique T. Atkins · Gerald S. Falchook · Apostolia M. Tsimberidou · David S. Hong · Meghana V. Trivedi · Razelle Kurzrock

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Abstract
Purpose We have observed severe, but rapidly reversible, hyperbilirubinemia in patients receiving hepatic arterial infusion (HAI) of oxaliplatin. We performed a retrospective analysis to characterize this unusual phenomenon.
Methods We reviewed the electronic medical records of 113 consecutive patients receiving HAI oxaliplatin to describe the associated hyperbilirubinemia.
Results Four of 113 patients (3.5 %) presented with transient, severe (grade 3/4) hyperbilirubinemia post-HAI oxaliplatin. Peak levels of total bilirubin within 10–16 h of starting HAI oxaliplatin were 4.6, 12.2, 12.8, and 21.2 mg/dL and declined rapidly (within 24 after stopping treatment). One out of four patients experienced severe abdominal pain, and another patient had an infusion reaction (hypertension and hypoxemia) that reversed after discontinuation of infusion. Total bilirubin was predominantly direct. No significant decline in hemoglobin or increase in alkaline phosphatase occurred. Increase in liver transaminases post-infusion was mild to moderate (grades 1–3) and was seen after HAI oxaliplatin regardless of the emerged hyperbilirubinemia.
Conclusions Severe hyperbilirubinemia is a rare but rapidly reversible adverse effect of HAI oxaliplatin and may be accompanied by an abdominal pain syndrome or infusion reaction. Treating physicians should be aware for the potential of this reaction. The mechanism of this unusual reaction merits further investigation.

Keywords Hepatic arterial infusion · Liver metastases · Oxaliplatin · Transient hyperbilirubinemia

Meghana V. Trivedi and Razelle Kurzrock are co-senior authors.

S. S. Garcia · M. V. Trivedi
Department of Clinical Sciences and Administration, University of Houston College of Pharmacy, 1441 Moursund St., Houston, TX 77030, USA

J. T. Atkins · G. S. Falchook · A. M. Tsimberidou · D. S. Hong · R. Kurzrock
Department of Investigational Cancer Therapeutics (Phase I Program), The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030, USA

M. V. Trivedi (✉)
Department of Pharmacological and Pharmaceutical Sciences, University of Houston College of Pharmacy, 1441 Moursund St., Houston, TX 77030, USA
e-mail: mtrivedi@central.uh.edu

Present Address:
R. Kurzrock
Department of Medicine, Hematology-Oncology Division, The University of California San Diego Moores Cancer Center, 3855 Health Sciences Drive, La Jolla, CA 92093, USA

Introduction

Oxaliplatin is a platinum-based cytotoxic chemotherapeutic drug indicated for the treatment of colorectal cancer [1]. Hepatic arterial infusion (HAI) of oxaliplatin has shown clinical activity and a tolerable toxicity profile in patients with liver metastases [2, 3]. Randomized trials are still needed to establish the role of HAI oxaliplatin on improving outcomes [4–8]. Commonly reported toxicities of HAI oxaliplatin include neutropenia, thrombocytopenia, neurotoxicity, hepatotoxicity, and abdominal pain [3, 6, 9].

In previous studies, a small percentage of patients (4–10 %) experience NCI-CTC grade 3 or 4 hyperbilirubinemia with HAI infusion [4, 9]; the presentation of this

adverse effect and its relationship to drug versus disease has not been reported. A small percentage of patients may also experience severe abdominal pain or pain syndrome at the time of infusion, which can persist despite dose reductions or prolonged infusion times and may require the use of opioid analgesics or other means of pain management [7, 10]. In general, this pain resolves rapidly if the infusion is discontinued.

In our review of 113 patients treated with HAI oxaliplatin, we observed severe hyperbilirubinemia accompanying infusion in four individuals (3.5 %). In these patients, the rise in total bilirubin was steep and transient, and the decline occurred rapidly after stopping the drug. In two patients, the hyperbilirubinemia was asymptomatic, while the other two experienced either severe abdominal pain syndrome or an infusion reaction.

Methods

One hundred and thirteen consecutive patients with metastatic malignancy to the liver receiving HAI oxaliplatin, starting in July 2009 in the Investigational Cancer Therapeutics Department, were assessed. Data were extracted from the electronic medical record system. This study and all treatments were conducted in accordance with MD Anderson and University of Houston Institutional Review Board guidelines.

Patient demographics (age, gender, race, and primary malignancy) were collected for all patients receiving HAI oxaliplatin. Once the cases of transient severe (grade 3/4) hyperbilirubinemia were identified, the following additional information was collected: date of metastatic disease diagnosis, prior therapies for metastatic disease, chemotherapy regimen with HAI oxaliplatin, duration of HAI infusion, and concomitant medications. Additional laboratory values recorded were direct and indirect bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, lactate dehydrogenase, albumin, total protein, and hemoglobin. Grades 3 and 4 severity of hyperbilirubinemia were defined based on NCI CTCAE (version 4.03) and were characterized by 3–10 × upper limit of normal (ULN) and >10 × ULN values of bilirubin, respectively [11]. ULN for total bilirubin was considered 1.0 mg/dL.

We also performed drug interaction analysis using Thomson Reuters Micromedex® and Elsevier Clinical Pharmacology® [12, 13]. A systematic literature search on reports of drug-induced hyperbilirubinemia using patient's chemotherapy regimen and concomitant medications was also performed using the following expanded Medical Subject Headings (MeSH) terms: "hyperbilirubinemia" and "generic name of the drug" in PubMed (1966–August 2012).

Results

Patient demographics

One hundred and thirteen patients with liver metastases received HAI oxaliplatin combination therapy. Median age was 59 years (range, 20–84 years), and 58 of the patients

Table 1 Patient demographics and characteristics

	All patients ($N = 113$)	Patients with transient severe hyperbilirubinemia ($N = 4$)	Patients without transient severe hyperbilirubinemia ($N = 109$)
Age in years: median (range)	59 (20–84)	53 (40–56)	60 (20–84)
Gender: *N* (%)			
Men	58 (51)	1 (25)	57 (52)
Women	55 (49)	3 (75)	52 (48)
Race: *N* (%)			
Caucasian	69 (61)	2 (50)	67 (61)
Black	23 (20)		23 (21)
Hispanic	17 (15)	2 (50)	15 (14)
Asian	3 (3)		3 (3)
Other	1 (1)		1 (1)
Primary malignancy: *N* (%)			
Colorectal	71 (63)	4 (100)	67 (62)
Breast	4 (4)		4 (4)
Cholangiocarcinoma	5 (4)		5 (5)
Pancreatic	5 (4)		5 (5)
Rectal	5 (4)		5 (5)
Other	23 (21)		23 (21)

(51 %) were men (Table 1). The majority of patients was Caucasian (61 %) and had colorectal cancer (63 %). Four of these patients experienced transient, severe (grade 3/4) hyperbilirubinemia. These four patients were 40, 51, 54, and 56 years old and three of them were women (Table 1). All four patients had colorectal cancer as their primary diagnosis, and all were previously treated with intravenous oxaliplatin without a similar reaction.

Presentation of transient hyperbilirubinemia

Patient 1 was a 51-year-old Caucasian woman diagnosed with *BRAF*-V600E mutant colorectal cancer in December of 2006. She later developed metastatic disease to the liver and lungs. Prior therapies for metastatic disease included FOLFOX regimen (5-fluorouracil + leucovorin + oxaliplatin), bevacizumab, irinotecan, cetuximab, and a *BRAF* inhibitor. She received HAI oxaliplatin (140 mg/m^2), IV 5-fluorouracil (325 mg/m^2), and leucovorin (200 mg/m^2) on day 1 and bevacizumab (10 mg/kg) and cetuximab (125 mg/m^2) on day 2 for a total of seven cycles. Pre-treatment total bilirubin was 0.7 mg/dL (direct: 0.1 mg/dL; indirect: 0.6 mg/dL) (Fig. 1a). Transient hyperbilirubinemia was observed during all cycles (Fig. 1a). The highest increase in total bilirubin occurred in cycle 6 (from 0.8 mg/dL pre-dose to 12.2 mg/dL 11-h post-infusion) (Table 2). Total bilirubin returned to 3.5 mg/dL on day 4 and was 0.7 mg/dL on day 31 before the start of the next cycle (Table 2). The patient had no symptoms related to the elevated bilirubin, and an ultrasound of the liver showed only known underlying liver metastases without significant intrahepatic biliary duct dilatation. In cycle 6, AST increased from 67 IU/L before treatment to 483 IU/L, and ALT from 49 to 273 IU/L, both 2 days post-infusion and returned to baseline after 15 days (Table 2). Alkaline phosphatase was 638 IU/L before HAI oxaliplatin and decreased to 301 IU/L at the time of total bilirubin of 8.4 mg/dL on day 3 (Table 2). No significant changes in lactate dehydrogenase, albumin, total protein, and hemoglobin were noted (data not shown). The concomitant medications, listed in Table 3, were not found to contribute to drug interactions or drug-induced hyperbilirubinemia observed in this patient. The patient had stable disease for seven cycles before discontinuation of therapy due to disease progression.

Patient 2 was a 56-year-old Hispanic woman diagnosed in December 2005 with colorectal cancer and liver metastases. Prior therapies for metastatic disease included: XELOX regimen (capecitabine + oxaliplatin) + bevacizumab, chemoradiation + capecitabine, FOLFOX regimen + bevacizumab, FOLFIRI regimen (5-fluorouracil + leucovorin + irinotecan) + cetuximab, irinotecan + cetuximab, and selective internal radiation spheres radioembolization. She received HAI oxaliplatin (140 mg/m^2) and 5-fluorouracil (1,750 mg/m^2) on day 1 and an IV dose of bevacizumab (10 mg/m^2) on day 2 for a total of 5 cycles. Pre-treatment total bilirubin was 3 mg/dL (direct: 2.1 mg/dL; indirect: 0.9 mg/dL) (Fig. 1b). Grade 3/4 transient hyperbilirubinemia was experienced in cycles 2, 4, and 5 (Fig. 1b). The most pronounced increase in total bilirubin occurred in cycle 4 (from 2.6 mg/dL pre-treatment to 21.4 mg/dL 14-h post-infusion) (Table 2). Subsequent values collected 6 h after the observed peak bilirubin revealed a total bilirubin of 19.1 mg/dL (direct: 15.2 mg/dL; indirect: 3.9 mg/dL) (Table 2). Total bilirubin returned to 7.7 mg/dL on day 5 and was 4.1 mg/dL on day 21, before the start of the next cycle. The patient had no symptoms related to elevated bilirubin, and ultrasound of the liver showed cholelithiasis and widespread metastases, but no evidence of intrahepatic biliary dilatation. In cycle 4, a modest increase occurred in AST from 113 IU/L before treatment to 180 IU/L and ALT from 60 to 80 IU/L, both 14-h post-infusion and returned to near pre-treatment values after 20 days (Table 2). No significant changes in lactate dehydrogenase, albumin, total protein, and hemoglobin were noted (data not shown). Alkaline phosphatase levels were not available. The concomitant medications are listed in Table 3 and were not found to contribute to drug interactions or drug-induced hyperbilirubinemia observed in this patient. After five cycles, the patient voluntarily discontinued enrollment in the study while still stable (25 % decrease in tumor size).

Patient 3 is a 54-year-old Caucasian man with *KRAS*-positive colorectal cancer with metastases to the liver diagnosed in May 2008. Prior therapies for metastatic disease included modified FOLFOX-6 with bevacizumab, and FOLFIRI with and without bevacizumab. He received HAI oxaliplatin (140 mg/m^2) and 5-fluorouracil (1,750 mg/m^2) on day 1 and an IV dose of bevacizumab (10 mg/kg) on day 2 for 5 cycles. Pre-treatment total bilirubin was 0.8 mg/dL (direct: 0.5 mg/dL; indirect: 0.3 mg/dL) (Fig. 1c). Grade 3 transient hyperbilirubinemia was experienced during cycles 3 and 5. The greatest increase in total bilirubin occurred in cycle 5 (from 0.3 mg/dL pre-dose to 4.6 mg/dL 10-h post-infusion) (Table 2). Direct bilirubin and indirect bilirubin were not documented at the time of elevation. On day 10, total bilirubin returned to 0.8 mg/dL (Table 2). No ultrasound was performed. This patient also developed an acute abdominal pain syndrome (10/10 on the institutional pain scale) during the HAI oxaliplatin infusion. Hydromorphone was given. Pain returned to baseline after the infusion was stopped. In cycle 5, increases in AST from 81 IU/L before treatment to 554 IU/L and in ALT from 15 to 134 IU/L occurred on day 3 and declined by day 10 (Table 2). No significant changes in lactate dehydrogenase, albumin, total protein, and

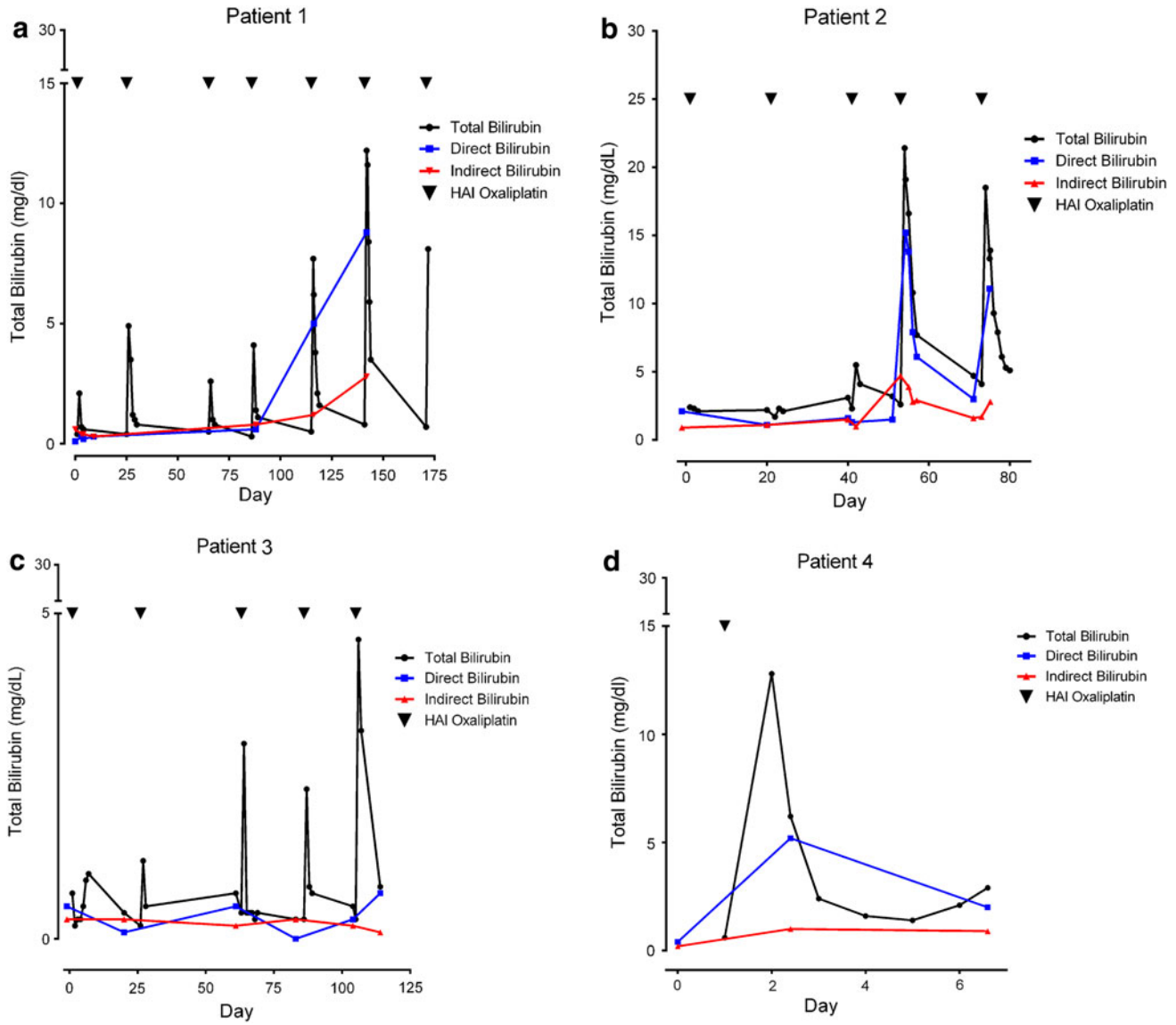

Fig. 1 Total bilirubin over the course of treatment in patients 1 (**a**), 2 (**b**), 3 (**c**), and 4 (**d**) Total, direct, and indirect bilirubin levels were measured throughout HAI oxaliplatin treatment. X-axis: Duration of HAI oxaliplatin therapy (in days); Y-axis: Concentration of total (*opened circle*), direct (*filled square*), and indirect (*filled diamond*) bilirubin (mg/dL). Testing was performed using CLIA-approved laboratory methods. Grade 3/4 transient hyperbilirubinemia occurred within 10–16-h post-infusion and started to decline within 24-h post-infusion. Total bilirubin levels were primarily comprised of direct bilirubin at times of elevation

hemoglobin were noted (data not shown). Values for alkaline phosphatase were not available. The concomitant medications are listed in Table 3 and were not found to contribute to drug interactions or drug-induced hyperbilirubinemia observed in this patient. After five cycles, the patient had slight interval reduction in the size of liver metastases before he withdrew consent.

Patient 4 was a 40-year-old Hispanic woman diagnosed in early 2006 with colorectal cancer, which was found to have metastasized to the liver later that year. Prior therapies for metastatic disease included: FOLFOX + bevacizumab, 5-fluorouracil + bevacizumab, FOLFIRI + bevacizumab, radiofrequency ablation, irinotecan + bevacizumab + cetuximab (subsequently substituted for panitumumab), capecitabine + cetuximab + bevacizumab, gemcitabine-based chemotherapy (other agents unknown), chemoembolization of the right hepatic arterial system with mitomycin, cisplatin + doxorubicin, and most recently, mitomycin + capecitabine. This patient was scheduled to receive HAI oxaliplatin (140 mg/m^2) and 5-fluorouracil (1750 mg/m^2) on day 1 and an IV dose of bevacizumab (10 mg/kg) on day 2. However, during the HAI oxaliplatin infusion (~90 min after the start of infusion), she experienced a reaction characterized by

Table 2 Total bilirubin and other pertinent laboratory values at baseline and post-infusion during selected cycles associated with transient severe hyperbilirubinemia

	Total bilirubin (mg/dl)	Direct bilirubin (mg/dL)	Indirect bilirubin (mg/dL)	AST (IU/L)	ALT (IU/L)	Alkaline phosphatase (IU/L)
Patient 1						
Day 0	1	–	–	91	72	638
Cycle 6 baseline	0.8	–	–	67	49	–
Day 2	12.2*	–	–	214	52	–
Day 2	11.6	8.8	2.8	351	96	–
Day 3	8.4	–	–	483	225	301
Day 3	5.9	–	–	–	273	–
Day 4	3.5	–	–	284	223	–
Day 16	1.3	0.5	0.8	92	62	820
Day 31	0.7	–	–	84	49	–
Patient 2						
Cycle 4 baseline	2.6	–	–	113	60	–
Day 2	21.4*	–	–	180	80	–
Day 2	19.1	15.2	3.9	–	–	–
Day 3	16.6	13.8	2.8	143	77	–
Day 4	10.8	7.9	1.6	135	90	–
Day 5	7.7	6.1	–	198	111	–
Day 21	4.1	–	–	130	69	–
Patient 3						
Cycle 5 baseline	0.3	–	–	81	15	–
Day 2	4.6*	–	–	241	20	–
Day 3	3.2	–	–	554	134	–
Day 10	0.8	0.7	0.1	61	70	–
Patient 4						
Cycle 1 baseline	0.6	0.4	0.2	40	18	416
Day 2	12.8*	–	–	168	28	–
Day 2	6.2	5.2	1	103	12	–
Day 3	2.4	–	–	61	21	–
Day 4	1.6	–	–	80	16	–
Day 5	1.4	–	–	52	18	–
Day 6	2.1	–	–	42	26	–
Day 6	2.9	2	0.9	46	26	325
Day 35	1	0.5	0.5	69	32	575

Baseline values are on day 1 of HAI oxaliplatin therapy; Baseline levels were drawn before HAI oxaliplatin was administered

* Signifies peak total bilirubin of respective cycle

– Denotes values not documented

AST aspartate aminotransferase, *ALT* alanine aminotransferase

oxygen desaturation and hypertension (190/95 mmHg). Infusion was promptly stopped and she was treated with hydrocortisone and hydralazine. Her pre-treatment total bilirubin was 0.6 mg/dL (direct: 0.4 mg/dL; indirect: 0.2 mg/dL) (Fig. 1d) but rose to 12.8 mg/dL 16-h post-dose (Table 2). Subsequent values collected 9 h after the observed peak bilirubin revealed total bilirubin of 6.2 mg/dL (direct: 5.2 mg/dL; indirect: 1 mg/dL). Total bilirubin declined to 2.9 mg/dL on day 6 and 1.0 mg/dL on day 35 (Table 2). No intermediate bilirubin values were collected. No ultrasound was performed. An increase in AST from 40 IU/L at baseline to 168 IU/L occurred 14-h post-infusion and was reversed to near normal levels by day 6 (Table 2). The alkaline phosphatase decreased from 416 IU/L at baseline to 325 IU/L on day 6. No significant changes in ALT (Table 2), lactate dehydrogenase, albumin, total protein, and hemoglobin were noted (data not shown). The concomitant medications are listed in Table 3 and were not found to contribute to drug interactions or drug-induced hyperbilirubinemia observed in this patient. The patient was taken off the protocol due to the reaction.

Table 3 Concomitant medications during selected cycles with severe hyperbilirubinemia

Patient 1 (cycle 6)	Patient 2 (cycle 4)	Patient 3 (cycle 5)	Patient 4 (cycle 1)
Alprazolam	Propoxyphene	Bevacizumab	Alprazolam
Bupropion	Lorazepam	Dexamethasone	Fentanyl transmucosal
Dicyclomine		Famotidine	Fentanyl patch
Esomeprazole		Ferrous sulfate	Hydrocodone–homatropine
Irbesartan/		Gabapentin	Lorazepam
HCTZ[a]		Hydrocodone/	Metoprolol
Levothyroxine		Acetaminophen	
Naproxen		Levothyroxine	
Prochlorperazine		Multivitamin	
Ropinirole		Nicotine-transdermal	
Trazodone		Olanzapine	

[a] Hydrochlorothiazide

Discussion

Four of 113 patients (3.5 %) with metastatic disease to the liver presented with transient severe hyperbilirubinemia during HAI oxaliplatin treatment. The total bilirubin levels in these patients rose to 4.6, 12.2, 12.8, and 21.4 mg/dL, respectively, within 10–16-h post-infusion and started to decline rapidly in less than 24 h after the infusion. In two patients, the bilirubin rise was asymptomatic, while one patient experienced 10/10 abdominal pain and another had oxygen desaturation and hypertension. The above symptoms reversed upon discontinuation of the infusion.

While rare cases of oxaliplatin-induced hemolysis have been reported, hemolysis was ruled out as a cause of the transient severe hyperbilirubinemia because there were no significant changes in hemoglobin (data not shown) and the hyperbilirubinemia observed was predominantly direct (Table 2) [14]. Capecitabine-induced hyperbilirubinemia is a well-known adverse effect and is possibly the result of hemolysis [15]. However, the elevated total bilirubin from capecitabine was primarily indirect, which differs from what we report here for HAI oxaliplatin. The high bilirubin levels were also not due to Gilbert's syndrome, since this syndrome presents with mildly elevated levels of indirect bilirubin due to a genetic polymorphism in the *UGT-1A1* gene [16].

Hepatitis is a common toxicity associated with HAI chemotherapy and may be evidenced by an elevation of liver enzymes or bilirubin [17]. Hepatitis secondary to HAI chemotherapy is reported to occur in as many as 42 % of patients [18]. Our patients did experience mild–moderate elevation in ALT and AST, but this was observed to a similar extent in most patients treated with HAI oxaliplatin regardless of transient severe hyperbilirubinemia and is therefore unlikely to be related to hyperbilirubinemia.

One of our patients experienced a severe, but reversible, abdominal pain syndrome during HAI oxaliplatin infusion. This pain syndrome has previously been reported in a small subset of patients receiving HAI oxaliplatin and may occur without hyperbilirubinemia [4–7]. One explanation for pain syndrome is postulated to be the result of excitation of visceral pain sensors within the biliary system [19]. Cold-induced dysesthesias, including severe laryngeal spasms and jaw tightness, have been reported with oxaliplatin [20, 21]. Whether such spasms intra-abdominally could account for abdominal pain is not known.

The rapid rise and fall in bilirubin is an unusual phenomenon and to our knowledge has not previously been described as a drug-induced effect. The fact that the bilirubin was predominantly direct suggests that the mechanism could involve an effect on the bile ducts. However, in the two patients with available data, alkaline phosphatase paradoxically decreased. Since a rise in alkaline phosphatase is believed to be a sensitive indicator of bile duct blockade, the etiology of the hyperbilirubinemia in our patients remains unclear.

In conclusion, four of 113 patients (3.5 %) treated with HAI oxaliplatin experienced severe transient hyperbilirubinemia (mainly direct) with levels increasing as high as 21.4 mg/dL after infusion. This phenomenon was asymptomatic in two patients, while the other two experienced either a severe abdominal pain syndrome or an infusion reaction with hypertension and oxygen desaturation. Treating physicians should be aware of this significant but reversible reaction. The mechanism of this unusual hyperbilirubinemia remains unclear.

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