

# Chemotherapy in patients with hepatobiliary cancers and abnormal hepatic function

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*Contributions:* (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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**Abstract:** Sorafenib and cisplatin plus gemcitabine currently represent first-line treatment standards in advanced hepatocellular carcinoma and biliary cancer, respectively. Conventional cytotoxic agents (monotherapy or combination therapy) have demonstrated activity in the second-line setting or in those in which first-line agents are contraindicated. A strategy for safe yet effective administration of such systemic therapies in patients with advanced hepatobiliary cancer and abnormal liver function needs to be strongly considered. Here, we highlight the safety and tolerability of systemic therapies routinely used for the treatment of advanced hepatobiliary cancer in patients with hepatic dysfunction. Based on data from available clinical studies, we review dosing strategies recommended for chemotherapy and targeted therapy in those with liver dysfunction. Dose modifications for many agents in this population remain empiric due to limited clinical evidence. Future dedicated phase I studies are needed to provide further dosing considerations for combination therapy in those with abnormal liver function in which data is lacking.

**Keywords:** Biliary cancer; hepatocellular carcinoma; abnormal liver function; chemotherapy

Submitted Apr 28, 2016. Accepted for publication Jul 29, 2016.

doi: 10.21037/jgo.2016.09.17

View this article at: <http://dx.doi.org/10.21037/jgo.2016.09.17>

## Introduction

Hepatocellular carcinoma (HCC) and biliary tract cancer are among the leading causes of cancer death in the United States with an estimated 39,230 new cases and 27,170 deaths in both men and women in 2016 (1). The combination of cisplatin + gemcitabine represents the standard first-line therapy in advanced biliary cancer (ABC) based on survival advantages conferred over gemcitabine alone in the phase III ABC-02 trial (2). In the event cisplatin is contraindicated, i.e., renal dysfunction, alternative first-line regimens exist. Gemcitabine + capecitabine has demonstrated activity in phase II trials in ABC (3,4). Several phase II trials have similarly shown responses to gemcitabine + 5-fluorouracil (5-FU) + leucovorin (LV) in unresectable or metastatic

biliary cancer (5-7). Another option includes gemcitabine + oxaliplatin, which has been investigated in phase II trials, though this combination is often associated with increased myelosuppression and neurotoxicity compared to cisplatin + gemcitabine (8-10). For those who have progressed through first-line chemotherapy, best supportive care (BSC) remains an acceptable standard in ABC though second-line chemotherapy may offer some benefits (11). Capecitabine monotherapy, 5-FU/LV + oxaliplatin (FOLFOX), 5-FU/LV + irinotecan (FOLFIRI) represent options with activity in the second-line treatment of ABC (12-15).

In unresectable or metastatic HCC, sorafenib has been established as a first-line standard therapy given its superiority over BSC in 2 separate phase III trials in patients with Child-Pugh A liver function (16,17). While previously

considered a standard therapy in inoperable HCC, doxorubicin demonstrated significant toxicities (neutropenia and cardiotoxicity) that outweighed its modest benefits in this population (18). Moreover, FOLFOX represents a more preferred first-line option over doxorubicin given the improved progression-free survival (PFS) and overall response rates (ORRs) seen with FOLFOX4 *vs.* single-agent doxorubicin in a phase III trial involving Asian patients with advanced HCC (19).

The majority of patients with HCC and biliary cancer present with advanced disease (20,21). The intrinsic liver dysfunction associated with hepatobiliary cancer often presents a challenge to the administration of the aforementioned systemic therapies in the treatment of advanced disease. In addition, chemotherapy and targeted therapy-induced hepatotoxicity can further complicate the treatment in these patients. The potential toxic effects of chemotherapy (including the majority of agents used in the treatment of advanced hepatobiliary cancer) on the liver have been extensively reviewed (22,23). Instead, this review will focus on dosage considerations for chemotherapy and targeted therapy in patients with abnormal hepatic function. Specifically, we review available clinical data that offer recommendations for dosing strategies, in the setting of liver dysfunction, of systemic therapies used in treating advanced hepatobiliary cancer.

### **Chemotherapy and targeted therapy in patients with liver dysfunction**

There is a growing body of clinical evidence to recommend dosing guidelines based on serum liver biochemical tests involving agents used in the treatment of advanced hepatobiliary cancer in patients with liver dysfunction (Tables 1-3).

#### **Gemcitabine**

An early phase I trial investigated gemcitabine at a starting dose of 800 mg/m<sup>2</sup> 30-minute infusion every week for 3 weeks followed by 1 week off in 43 patients stratified by aspartate aminotransferase (AST)  $\geq 2$  times the upper limit of normal (ULN), total bilirubin of 1.6–7.0 mg/dL with any AST level, and serum creatinine of 1.6–5.0 mg/dL (24). The most frequent dose-limiting toxicity (DLT) was hyperbilirubinemia ( $\geq 1.5$  times baseline) seen in 7 patients in the cohort with a median bilirubin of 2.7 mg/dL (range, 1.7–5.7 mg/dL). Hyperbilirubinemia was transient and

often lasting  $< 1$  week in the majority of affected patients. In this same cohort, 3/8 patients experienced DLTs at the 800 mg/m<sup>2</sup> dosing level while 8/10 experienced DLTs at the 950 mg/m<sup>2</sup> dosing level. There were no apparent differences in pharmacokinetics (PKs) compared to historical controls. The investigators concluded that no dose reductions of gemcitabine are required in those with elevated transaminases or creatinine, but in those with elevated bilirubin, gemcitabine should be reduced to 800 mg/m<sup>2</sup> initially with subsequent escalation in the absence of DLTs (Table 1). In a recent retrospective case series, all 7 patients with total bilirubin  $\geq 4.5$  mg/dL received full doses of 1,000 mg/m<sup>2</sup> gemcitabine safely without further worsening of liver function and only 1 of 7 developed significant thrombocytopenia necessitating a dose to be held (42). The authors recommended that no initial dose reduction is needed in patients with impaired liver function receiving gemcitabine though close monitoring is preferred.

#### **Cisplatin**

Cisplatin and carboplatin are primarily excreted by the kidneys and do not require dose modifications in patients with abnormal hepatic function. No formal studies exist but a pilot study investigating cisplatin 75 mg/m<sup>2</sup> every 21 days + vinorelbine 20 mg/m<sup>2</sup> on days 1 and 8 every 21 days in 11 patients with severe liver dysfunction caused by metastatic breast cancer with serum bilirubin  $> 1.5$  times the ULN showed improvement in liver function tests in 10 patients by day 40 of treatment (43). No dose modifications were needed and there were no significant adverse events (AEs) related to hepatotoxicity.

#### **Fluorouracil**

A phase I trial stratified 64 patients to receive weekly 24-hour infusions of 1,000–2,600 mg/m<sup>2</sup> 5-FU + LV 500 mg/m<sup>2</sup> into 3 cohorts: elevated creatinine ( $> 1.5$  mg/dL) but normal bilirubin, bilirubin  $> 1.5$  mg/dL but  $< 5.0$  mg/dL with normal creatinine, and bilirubin  $\geq 5.0$  mg/dL with normal creatinine (25). Across all 3 cohorts, there was no apparent difference in likelihood of experiencing DLTs and infusional 5-FU (2,600 mg/m<sup>2</sup>) can be safely administered without dosage adjustments (Table 1). There was no significant relationship between serum bilirubin or creatinine and 5-FU clearance.

#### **Capecitabine**

An open-label, multicenter prospective study investigated

**Table 1** Dosing strategies for single agents used in the treatment of advanced hepatobiliary cancer in patients with abnormal hepatic function

Agent	Size	Dosing	Bilirubin range evaluated	Dosing recommendations	Ref.
Gemcitabine	43	Initial 800 mg/m <sup>2</sup> IV weekly × 3 weeks then 1 week off	1.6–7.0 mg/dL	Transaminitis: no dosage reduction  Hyperbilirubinemia (up to 7 mg/dL): reduce to 800 mg/m <sup>2</sup> initially, escalate as tolerated	Phase I (24)
Cisplatin	NA	NA	No published studies	No dose modifications needed; mainly renal excretion	NA
Fluorouracil	64	24-hour infusion of 5-FU 1,000–2,600 mg/m <sup>2</sup> + LV 500 mg/m <sup>2</sup> weekly	>1.5–≥5.0 mg/dL (upper limit NR)	No dose modifications needed	Phase I (25)
Capecitabine	27	Oral capecitabine 1,255 mg/m <sup>2</sup>	0.9–28.3 mg/dL	No dose modifications needed	PS (26)
Oxaliplatin	60	60 to 130 mg/m <sup>2</sup> oxaliplatin 2-hour infusion every 3 weeks	Mean 0.5–10.2 mg/dL	No dose modifications needed	PS (27)
Doxorubicin	96	60 mg/m <sup>2</sup> infusion over 1–5 minutes every 3 weeks	NR	Total bilirubin 2.0–3.0 mg/dL: 50% dose reduction  Total bilirubin 3.0–5.0 mg/dL: 75% dose reduction Total bilirubin >5.0 mg/dL: withhold doxorubicin	PS (28)
Irinotecan	33	100–350 mg/m <sup>2</sup> 30-minute infusion every 3 weeks	0.2–5.7 mg/dL	Total bilirubin ≤1.5 × ULN: 350 mg/m <sup>2</sup>  Total bilirubin 1.5–3.0 × ULN: 200 mg/m <sup>2</sup>  Total bilirubin ≥3.1 × ULN: irinotecan not recommended	Phase I (29)
Irinotecan	35	115–350 mg/m <sup>2</sup> 90-minute infusion every 3 weeks	Direct bilirubin 1.0–7.0 mg/dL	Elevated AST (AST ≥3 × ULN): not associated with increased risk of toxicity  Elevated direct bilirubin (1.0–7.0 mg/dL): dose reduction recommended	Phase I (30)
Irinotecan	42	40–75 mg/m <sup>2</sup> 90-minute infusion weekly for 4 weeks every 6 week cycles	≤1.5–5.0 × ULN	Total bilirubin 1.5–3.0 × ULN and ALT/AST ≤5.0 × ULN: 60 mg/m <sup>2</sup>  Total bilirubin 3.1–5.0 × ULN and ALT/AST ≤5.0 × ULN: 50 mg/m <sup>2</sup>  Total bilirubin ≤1.5 × ULN and ALT/AST 5.1–20.0 × ULN: 60 mg/m <sup>2</sup>  Total bilirubin 1.5–3.0 × ULN and ALT/AST 5.1–20.0 × ULN: 40 mg/m <sup>2</sup>	Phase I (31)

IV, intravenous; NA, not applicable; 5-FU, 5-fluorouracil; LV, leucovorin; NR, not reported; PS, prospective study; ULN, upper limit of normal; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

PK parameters following administration of a single oral dose of capecitabine (1,255 mg/m<sup>2</sup>) in 14 patients with normal liver function and 13 patients with liver dysfunction secondary to liver metastases (mean bilirubin 6.5 mg/dL; range, 0.9–28.3 mg/dL) and demonstrated that liver dysfunction had no clinically significant influence on the

PK parameters of capecitabine and its metabolites (26). No clinically significant differences in AEs were observed between patients with or without hepatic impairment (*Table 1*). Hyperbilirubinemia is a known capecitabine-associated adverse event, even in patients with normal hepatic function. We have therefore replaced this agent,

**Table 2** Dosing strategies for combination agents used in the treatment of advanced hepatobiliary cancer in patients with abnormal hepatic function

Agent	Size	Dosing	Bilirubin range evaluated	Dosing recommendations	Ref.
Cisplatin + gemcitabine	33	Initial cisplatin 25 mg/m <sup>2</sup> days 1 and 8 + gemcitabine 1,000 mg/m <sup>2</sup> days 1 and 8 every 3 weeks up to 8 cycles	1.87–16.73 mg/dL	Can be safely administered in PS 0-1 patients with serum bilirubin $\geq 1.5 \times$ ULN due to biliary obstruction despite optimal stenting; no benefit in unfit patients with liver metastases-related jaundice	RS (32)
Gemcitabine + capecitabine	12	Gemcitabine 1,000 mg/m <sup>2</sup> 30-minute infusion on days 1 and 8 + capecitabine 650 mg/m <sup>2</sup> oral twice daily on days 1–14 every 21 days	$\leq 0.9$ – $>4.7$ mg/dL (upper limit NR)	Can be safely administered in patients with hepatic dysfunction (in those with total bilirubin $>4.7$ mg/dL, treat with capecitabine alone and add gemcitabine when hyperbilirubinemia improved)	PS (33)
Gemcitabine + oxaliplatin	56	Gemcitabine 1,000 mg/m <sup>2</sup> 100-minute infusion on day 1 + oxaliplatin 100 mg/m <sup>2</sup> 2-hour infusion on day 2 every 2 weeks	NR	Can be safely administered in group of patients with performance status $>2$ , total bilirubin $>2.5$ times the ULN (upper limit NR but in single-agent gemcitabine upper limit was 7 mg/dL), and/or having received prior chemotherapy	PS (8)
Capecitabine + oxaliplatin	1	Capecitabine 1,000 mg/m <sup>2</sup> oral twice daily on days 1–14 + oxaliplatin 130 mg/m <sup>2</sup> intravenous on day 1 every 21 days	Initial 10.9 mg/dL	Tolerated in patient with abnormal liver function secondary to metastatic gastric cancer	CR (34)
FOLFOX	11	FOLFOX4 or mFOLFOX6	3.5–22.5 mg/dL	Can be safely administered in patients with severe hepatic dysfunction (range, 3.5–22.5 mg/dL)	CR (35-41)
FOLFIRI	NA	NA	NA	No published studies	NA

PS, performance status or prospective study; RS, retrospective study; ULN, upper limit of normal; NR, not reported; CR, case report; FOLFOX, 5-fluorouracil + leucovorin + oxaliplatin; mFOLFOX6, modified 5-fluorouracil + leucovorin + oxaliplatin; NA, not applicable; FOLFIRI, 5-fluorouracil + leucovorin + Irinotecan.

**Table 3** Initial dosing of sorafenib based on liver dysfunction by CALGB 60301

Liver function parameters evaluated	Dosing recommendations
Total bilirubin $> ULN$ but $\leq 1.5 \times ULN$ and/or AST $> ULN$	400 mg twice daily
Total bilirubin $> 1.5 \times ULN$ to $\leq 3 \times ULN$ and any AST	200 mg twice daily
Total bilirubin $> 3 \times ULN$ to $\leq 10 \times ULN$ and any AST	Not recommended
Albumin $< 2.5$ mg/dL and any bilirubin/AST	200 mg daily

ULN, upper limit of normal; AST, aspartate aminotransferase.

when feasible, with 5-FU infusional therapy in the settings of patients with hepatic dysfunction.

### ***Oxaliplatin***

A dose-escalation trial enrolled 60 patients with advanced

solid tumors and normal-severe hepatic dysfunction (severe defined as bilirubin  $>3.0$  mg/dL) to receive 60 to 130 mg/m<sup>2</sup> oxaliplatin 2-hour infusion every 3 weeks (27). No DLTs were observed at the maximum tolerated dose (MTD) defined as 130 mg/m<sup>2</sup> oxaliplatin in the cohort with severe liver dysfunction. Additionally, abnormal liver function did

not correlate with platinum clearance. The investigators concluded that full doses of single-agent oxaliplatin can be safely administered in patients with liver dysfunction without the need for dosage adjustments (*Table 1*).

### ***Doxorubicin***

Although largely replaced by other standard therapies in the treatment of advanced HCC, doxorubicin has been associated with increased risk of toxicities in those with impaired liver function (*Table 1*). An early study enrolled 96 patients with predominantly pretreated malignancies to receive a planned dose of doxorubicin 60 mg/m<sup>2</sup> infusion over 1–5 minutes every 3 weeks (28). Notably, 8 patients with significant liver dysfunction experienced increased toxicities of severe mucositis (3 patients or 38%) and severe pancytopenia (all 8 patients). Liver dysfunction was shown to delay clearance of doxorubicin and increase plasma levels of doxorubicin and its metabolites by 4–5-fold. The investigators recommended a 50% dose reduction for total bilirubin of 2.0–3.0 mg/dL, a 75% dose reduction for bilirubin of 3.0–5.0 mg/dL, and to withhold doxorubicin for bilirubin >5.0 mg/dL. However, others have contended that the small number of patients with liver dysfunction in this study does not justify an indiscriminate dose reduction and argue for dose modification of doxorubicin only in the setting of total bilirubin >3.0 mg/dL (44). Given the lack of known activity of doxorubicin in cholangiocarcinoma and its limited activity in HCC, the authors recommend against its use in patients with severe hepatic dysfunction. Patients with HCC and bilirubin levels exceeding 3 mg/dL have not been shown to derive a clinical benefit from cytotoxic chemotherapy, specifically doxorubicin. Such patients may be best addressed with palliative intent.

### ***Irinotecan***

Several phase I trials have investigated the safety of irinotecan and its effects on PKs in patients with abnormal hepatic function (*Table 1*). One phase I trial enrolled 33 patients with refractory solid tumors and assigned irinotecan 350 mg/m<sup>2</sup> 30-minute infusion every 3 weeks to those with normal bilirubin and total bilirubin 1.1–1.5 times the ULN (29). Patients with bilirubin 1.51–3.0 times the ULN and ≥3.1 times the ULN were assigned to starting doses of 175 mg/m<sup>2</sup> and 100 mg/m<sup>2</sup> irinotecan, respectively. The recommended dose of irinotecan was 350 mg/m<sup>2</sup> in those with bilirubin ≤1.5 times the ULN. The recommended

dose of irinotecan in those with bilirubin 1.5–3.0 times the ULN was 200 mg/m<sup>2</sup>. Due to rapid progression of hepatic metastases and poor PS in patients with total bilirubin ≥3.1 times the ULN, dose escalation could not be carried out and dosing of irinotecan could not be recommended. Hyperbilirubinemia and elevated alkaline phosphatase (ALP) were associated with an exponential decrease in clearance of irinotecan and its metabolites (likely due to decreased biliary excretion).

A separate phase I trial enrolled 35 patients with varying degrees of liver dysfunction to receive 115–350 mg/m<sup>2</sup> of irinotecan 90-minute infusion every 3 weeks (30). In the cohort of patients with AST ≥3 times the ULN with normal bilirubin and serum creatinine, there were no DLTs at the 225 mg/m<sup>2</sup> dosing level. However, patients with direct bilirubin 1.0–7.0 mg/dL and any level of AST with normal serum creatinine (<1.6 mg/dL) experienced DLTs at 145 mg/m<sup>2</sup> of irinotecan and experienced higher relative exposure to irinotecan and SN-38 due to reduced clearance. This study confirmed that elevated bilirubin is associated with increased risk of toxicity from irinotecan and a dose reduction is recommended.

Another phase I trial investigated 40–75 mg/m<sup>2</sup> of irinotecan 90-minute infusion weekly for 4 weeks every 6 week cycles in 42 patients with varying degrees of hepatic dysfunction (31). The recommended dose of weekly irinotecan was 60 mg/m<sup>2</sup> for those with total bilirubin 1.5–3.0 times the ULN and alanine aminotransferase (ALT) to AST ratio (ALT/AST) ≤5.0 times the ULN, 50 mg/m<sup>2</sup> with total bilirubin 3.1–5.0 times the ULN and ALT/AST ≤5.0 times the ULN, 60 mg/m<sup>2</sup> with total bilirubin ≤1.5 times the ULN and ALT/AST 5.1–20.0 times the ULN, and 40 mg/m<sup>2</sup> with total bilirubin 1.5–3.0 times the ULN and ALT/AST 5.1–20.0 times the ULN. Increased serum bilirubin was a relatively strong indicator of reduced clearance of irinotecan and SN-38, more so than other biochemical markers of liver function given the eventual plateau of irinotecan and SN-38 area under the curve (AUC) values with increasing AST.

Given the limited safety data with every 3 week irinotecan dosing with bilirubin levels >3 mg/dL, the authors do not recommend this schedule in this patient population. If irinotecan is to be considered in patients with bilirubin levels between and 3 and 5 mg/dL, we recommend the use of a weekly regimen at 50 mg/m<sup>2</sup>/week as described by Schaaf *et al.* (31). Of note, no dedicated studies have been reported with FOLFIRI in patients with severe hepatic dysfunction to make firm recommendations.

**Cisplatin + gemcitabine**

A retrospective study of planned cisplatin (25 mg/m<sup>2</sup> days 1 and 8) gemcitabine (1,000 mg/m<sup>2</sup> days 1 and 8) every 3 weeks up to 8 cycles in the first-line treatment of ABC in 33 patients [performance status (PS) 0-1] with serum bilirubin  $\geq 1.5$  times the ULN due to biliary obstruction despite optimal stenting identified comparable rates of abnormal liver function tests (drug-related) to the non-jaundiced cohort in the ABC-02 trial (32). Full-dose cisplatin + gemcitabine was safely administered in the majority of patients with biliary obstruction-related jaundice (70%) and resulted in normalization of bilirubin in 68% of patients in this cohort (Table 2). On the contrary, cisplatin + gemcitabine did not appear to provide benefits in patients with poor PS and liver metastases-related jaundice when compared to those with biliary obstruction-related jaundice.

**Gemcitabine + capecitabine**

A recent prospective study investigated gemcitabine 1,000 mg/m<sup>2</sup> 30-minute infusion on days 1 and 8 + capecitabine 650 mg/m<sup>2</sup> oral twice daily on days 1–14 every 21 days in 12 patients with unresectable or metastatic pancreatic or biliary cancer (33). Eight patients had varying degrees of hepatic dysfunction (2 with total bilirubin of 0.9–2.3 mg/dL, 3 with total bilirubin of 2.3–4.7 mg/dL, and 3 with total bilirubin >4.7 mg/dL) due to liver metastases (50%) or extrahepatic cholestasis from tumor compression (50%). There was no significant correlation between hepatic function cohort and DLT leading to dose reduction or withholding of a dose (P=0.55). However, hepatic dysfunction was associated with reduced clearance of both gemcitabine and capecitabine and limited activity of gemcitabine due to decreased intracellular activation. In short, standard dosing of gemcitabine + capecitabine could be safely administered in patients with hepatic dysfunction though it was recommended that patient's with total bilirubin >4.7 mg/dL should be initially treated with single-agent capecitabine with gemcitabine added once hyperbilirubinemia improves (Table 2).

**Gemcitabine + fluorouracil**

The original phase I studies investigating the combination of gemcitabine + 5-FU in refractory or unresectable solid tumors enrolled patients with adequate hepatic function (as restrictive as total bilirubin  $\leq 1.5$  mg/dL) and renal function

(45-47). To our knowledge, there are no formal studies to date evaluating the safety of gemcitabine + 5-FU in patients with liver dysfunction; recommendations for dosing strategies in this population are similarly lacking.

**Gemcitabine + oxaliplatin**

A prospective study enrolled 56 patients with unresectable or metastatic ABC to receive gemcitabine 1,000 mg/m<sup>2</sup> 100-minute infusion on day 1 followed by oxaliplatin 100 mg/m<sup>2</sup> 2-hour infusion on day 2 every 2 weeks (8). A group of 23 patients were defined by PS >2, total bilirubin >2.5 times the ULN, and/or having received prior chemotherapy (group B); 13 patients in this group (57%) had total bilirubin  $\geq 2.5$  times the ULN. Tolerability to gemcitabine + oxaliplatin in group B was not significantly different from group A patients (normal counterparts), and the investigators concluded that this combination is safe in this cohort with abnormal liver function (Table 2). Formal dosing recommendations have not been evaluated in a dedicated study involving gemcitabine + oxaliplatin in the setting of liver dysfunction, however.

**Capecitabine + oxaliplatin**

Similarly, the combination of capecitabine + oxaliplatin has not been formally studied in patients with hepatic dysfunction in the phase I setting. A case report describing a patient with abnormal liver function secondary to metastatic gastric cancer (initial serum bilirubin 10.9 mg/dL) reported that capecitabine 1,000 mg/m<sup>2</sup> oral twice daily on days 1–14 + oxaliplatin 130 mg/m<sup>2</sup> intravenous (IV) on day 1 every 21 days can be safely administered in the setting of hepatic impairment (34). After 2 cycles of therapy, total bilirubin and alkaline phosphatase demonstrated near-normalization and no treatment-related grade  $\geq 3$  toxicities occurred during first 4 cycles of therapy.

**FOLFOX**

Several case reports involving 11 separate patients with metastatic colorectal cancer have shown that the administration of FOLFOX4 or mFOLFOX6 is safe and tolerated in patients with severe hepatic dysfunction (35-41). Total bilirubin levels ranged from 3.5–22.5 mg/dL and treatment with FOLFOX often resulted in dramatic improvements in hyperbilirubinemia as early as 1–2 cycles of therapy without significant toxicities (Table 2). Many of these patients also

achieved durable responses in their metastatic disease following treatment with FOLFOX.

### **FOLFIRI**

In a single-institution retrospective study, 156 patients with metastatic colorectal cancer treated with first-line FOLFIRI-based regimens were evaluated for liver toxicity (48). The majority of patients had liver involvement (64.74%) during the initiation of first-line therapy. Levels of AST, ALT, and alkaline phosphatase (AE) were all found to be significantly increased during first 3 months of treatment and the calculated R ratio was 3.96 (3.25–4.51). Twenty-five patients (16.02%) experienced course delays, 12 (7.69%) needed a dose reduction, and 3 (1.92%) stopped therapy due to significant liver toxicity. Of note, this study described patterns of liver toxicity in patients treated with a FOLFIRI-based backbone of chemotherapy. Dedicated safety evaluations of an exclusive FOLFIRI regimen in the phase I setting and formal dosing recommendations in patients with liver dysfunction are lacking.

### **Sorafenib**

A phase I study (CALGB 60301) enrolled 138 patients with various solid and hematologic malignancies and stratified patients to receive doses of oral sorafenib that ranged from 200 mg every other day to 400 mg twice daily depending on increasing severity of hepatic dysfunction or renal dysfunction (49). A single oral dose of 400 mg sorafenib was administered on day 1 to evaluate PKs, and one cohort was defined by normal renal and liver function. There was no significant association between AUCs of sorafenib or its major metabolite and cohort ( $P>0.05$ ). In the hepatic dysfunction cohort, DLTs included total bilirubin  $\geq 1.5$  times the baseline ( $n=10$ ), grade 3 diarrhea ( $n=1$ ), grade 3 fatigue ( $n=1$ ), grade 3 fatigue and reduction in creatinine clearance  $>10$  mL/min ( $n=1$ ), and grade 3 hypertension ( $n=1$ ). Accordingly, the investigators recommended a dose of sorafenib 400 mg twice daily in those with total bilirubin  $> \text{ULN}$  but  $\leq 1.5$  times the ULN and/or AST  $> \text{ULN}$ , 200 mg twice daily for total bilirubin  $>1.5$  times the ULN to  $\leq 3$  times ULN with any AST, not recommended for total bilirubin  $>3$  times the ULN to 10 times the ULN with any AST, and 200 mg daily for albumin  $<2.5$  mg/dL with any bilirubin/AST (Table 3).

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with Sorafenib (GIDEON) nonrandomized observational study enrolled  $>3,000$  patients with unresectable HCC treated with sorafenib  $\pm$  transarterial chemoembolization (TACE) and identified an overall survival of 21.6 months (95% confidence interval 18.0–not reached) with concomitant sorafenib and TACE *vs.* 9.7 months (95% confidence interval 9.2–10.4) in those not treated concomitantly (50). In a United States regional analysis, 543 patients were stratified into those who received TACE prior to initiating sorafenib (group A,  $n=158$ ), underwent TACE after initiating sorafenib (group B,  $n=29$ ), received TACE concurrently with sorafenib (group C,  $n=38$ ), and received sorafenib without TACE ( $n=318$ ). Notably, at least 35% of patients in all groups had Child-Pugh B or C liver function at the start of sorafenib therapy (51). The majority of patients in all groups received full-dose sorafenib initially, and the investigators concluded that these observations reflect the high degree of comfort in using sorafenib and TACE in those with abnormal liver function in real-life clinical settings.

### **Conclusions**

Treatment standards currently favor combination chemotherapy and targeted therapy, *i.e.* sorafenib, in ABC and advanced HCC, respectively. In second-line settings or those with contraindications to first-line agents, conventional cytotoxic agents (monotherapy or combination therapy) have demonstrated activity in advanced HCC and biliary tract cancer. In populations with hepatobiliary cancer and abnormal liver function, an appropriate strategy providing effective yet safe administration of such systemic agents needs to be strongly considered.

The majority of clinical trials (phase I–III) have historically excluded patients with predefined hepatic impairment, *i.e.*, abnormal serum liver function tests. Very little is often known regarding the appropriate starting doses of chemotherapy in patients with liver dysfunction. As a result, dose reductions commonly performed in clinical practice are often empiric with re-escalation of dose in the absence of DLTs. There is a growing body of phase I studies providing data on PKs and dosing strategies of chemotherapy in those with hepatic dysfunction. However, formal phase I studies on PKs and dosing recommendations of several combination regimens in those with hepatobiliary cancer and impaired liver function are still lacking. Furthermore, available dosing strategies often focus on initial dosing recommendations in those with abnormal

liver function tests. Guidelines on how long to withhold a dose and what dose to restart therapy are vague and such decisions are often empirically performed by the clinician.

Further dedicated phase I studies offering specific dosing strategies for agents routinely used for treating advanced hepatobiliary cancer in those with hepatic dysfunction are warranted, particularly in combination regimens when PKs and tolerability may be influenced by drug-drug interactions and liver metabolism. Retrospective analyses and case series may also provide additional information on safety and dosing strategies in those with abnormal liver function. Future studies should also incorporate other measures of liver function including AST, ALT, AP, and albumin beyond the standard total bilirubin to assess safety and dosing considerations in those with liver disease receiving chemotherapy. For now, an appropriate strategy for effective yet safe dosing of systemic therapies in patients with liver dysfunction will need to balance available safety data from clinical studies on one hand and a risks and benefits discussion between the clinician and patient on the other.

### Acknowledgements

None.

### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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**Cite this article as:** Gong J, Cho M, Fakhri M. Chemotherapy in patients with hepatobiliary cancers and abnormal hepatic function. *J Gastrointest Oncol* 2017;8(2):314-323. doi: 10.21037/jgo.2016.09.17