Chemotherapy-associated liver injury in colorectal cancer

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Abstract: Patients with colorectal cancer (CRC) have benefited significantly from advances in multimodal treatment with significant improvements in long-term survival. More patients are currently being treated with surgical resection or ablation following neoadjuvant or adjuvant chemotherapy. However, several cytotoxic agents that are administered routinely have been linked to liver toxicities that impair liver function and regeneration. Recognition of chemotherapy-related liver toxicity emphasizes the importance of multidisciplinary planning to optimize care. This review aims to summarize current data on multimodal treatment concepts for CRC, provide an overview of liver damage caused by commonly administered chemotherapeutic agents, and evaluate currently suggested protective agents.

Keywords: colorectal cancer, liver metastases, chemotherapy, hepatotoxicity, sinusoidal obstruction syndrome, chemotherapy-associated liver injury

Introduction

Colorectal cancer (CRC) is the fourth most common cancer in the United States (US) and the second leading cause of cancer-related deaths. Between 30% and 50% of CRC cases will either present with or develop liver metastases, and, of these, only 50% will have medically or surgically curable disease.[1,2] The mainstay of treatment for CRC is surgical resection with curative intent and neoadjuvant or adjuvant therapy. In the last decade, improvements in systemic therapy and surgical technique have resulted in improved survival rates for CRC patients.[3] This review is focused on the hepatotoxicity that develops as a result of systemic chemotherapy used to treat CRC, which often limits surgical options.

Treatments of CRC liver metastasis

The treatment of patients with metastatic CRC is typically multidisciplinary, with the mainstay of therapy being systemic chemotherapy. When surgical resection is an option, the treatment algorithm changes to include surgery with systemic chemotherapy either preceding or following resection. Three categories of patients with CRC liver metastases (CRLM) exist. In the first category, the hepatic metastases are considered resectable at the time of diagnosis. In the second, the hepatic metastases are potentially resectable but might require thorough pre-operative planning, which could include neoadjuvant therapy to decrease tumor burden, staged resections because of tumor burden and distribution of disease, the need for portal vein embolization to grow the liver remnant, and consideration of combination ablative and resection approaches. The third category of patients are typically deemed unresectable, but some of these patients will convert to potentially resectable with systemic therapy whereas others will not.[4–6] Importantly, in those patients with up-front resectable liver metastases, a subset will ultimately develop recurrent disease either in the liver alone or in extrahepatic sites. With the increased use of systemic therapies, impressive tumor response rates have been observed, allowing for improved resectability rates in patients with CRLM. The benefits include decrease in tumor size, control of micrometastatic disease, assessing response to chemotherapy, and potentially predicting potential of success for resection. However, with increased chemotherapy use, there has been better recognition of a wide range of hepatic toxicities associated with the use of systemic chemotherapy.

The risks of these therapies include liver toxicity, progression of disease while on therapy, secondary

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splenomegaly, and selection of resistant tumor clones.[7] As such, potential impaired liver function must be taken into account during pre-operative planning. In general, a liver remnant volume of >30% is needed for livers that have undergone chemotherapy associated changes.[8] Also, longer durations of preoperative chemotherapy are associated with a greater potential for liver toxicity and postoperative complications. Some investigators have suggested limiting chemotherapy to 4–6 cycles if a subsequent liver resection is planned.[9]

Types of liver injury from systemic chemotherapy used in CRLM

There are numerous reports of systemic chemotherapy used in CRLM causing liver injury, specifically with increased incidence of steatosis, steatohepatitis, and sinusoidal injury.[10–12] Steatosis refers to the accumulation of lipids within hepatocytes, and is considered an initial stage of nonalcoholic fatty liver disease (NAFLD). Various reasons for lipid accumulation have been suggested, which include excessive import of free fatty acids (FFAs), diminished hepatic export of FFAs, or impaired oxidation of FFAs.[13] Steatosis first leads to steatohepatitis, which is characterized by the development of liver cell injury in the form of ballooning. This then leads to fibrosis. Steatohepatitis can significantly impair baseline liver function and lead to cirrhosis and liver failure in selected patients.[14,15] Sinusoidal obstruction syndrome (SOS) differs from steatosis and steatohepatitis in that it results from damage to the endothelial cells that line the liver sinusoids that does not interfere directly with the function of hepatocytes. SOS was previously referred to as liver veno-occlusive disease, and was frequently observed with use of high-dose chemotherapy regimens for patients undergoing stem cell transplant. SOS itself is known to lead to hyperbilirubinemia, portal hypertension, development of ascites, and, occasionally, liver failure.[16,17]

Chemotherapeutic regimens used in CRLM and the type of liver injury they cause

Before 2000, the standard treatment for CRC was single agent 5-fluorouracil (5-FU) with leucovorin, and this yielded response rates of approximately 20%.[18] In the last 20 years, however, new chemotherapy regimens were developed and have increased response rates to approximately 50%.[19,20] The most commonly used CRLM chemotherapy regimens include oxaliplatin with 5-FU and leucovorin, known as FOLFOX, and irinotecan plus 5-FU and leucovorin, known as FOLFIRI. Previous studies have shown that the type of liver injury is regimen specific. For example, irinotecan-based regimens are associated with steatohepatitis, whereas oxaliplatin-based regimens are associated with sinusoidal injury (Table 1).[21–23] These toxicities are critical to understand as they may severely complicate liver directed ablative therapies [i.e. radiofrequency ablation (RFA)] or surgical resection, thereby compromising the individual oncologic treatment plans for these CRC patients.

An association between 5-FU and steatosis was first observed in both radiologic and pathologic studies.[12,24–26] As mentioned previously, there are a variety of methods by which FFAs accumulate within the liver. 5-FU-induced steatosis is thought to result from drug-induced mitochondrial dysfunction resulting in impairments of FFA oxidation. *In vitro* studies have showed that, in primary human hepatocytes, 5-FU administration caused a significant increase of intracellular FFA and triglyceride levels, not *via* de novo lipogenesis, but by limiting mitochondrial FFA oxidation. The mechanism may involve induction of acylcoenzyme A oxidase 1 (ACOX1). ACOX1 is the first and rate-limiting enzyme of the peroxisomal fatty acid oxidation (FAO) pathway; chronic activation of peroxisomal FAO can cause oxidative stress and be detrimental to mitochondrial FAO.[27] 5-FU administration has been shown to increase the expression of ACOX1, leading to higher levels of pro-inflammatory genes and resulting in increase in reactive oxygen species (ROS), which induces one of the antioxidant enzymes, heme oxygenase 1, to mitigate liver injury.[28,29] 5-FU also induces expression of proinflammatory genes and immune cell infiltration.[28] Steatosis can progress to steatohepatitis from impaired mitochondrial FAO, ROS, and inflammatory cell infiltration.

Chemotherapy-associated steatohepatitis (CASH) is well described in CRLM patients receiving irinotecan-based therapies. There are two main studies that have shown this. The first study, which includes 94 patients treated with 5-FU and irinotecan and 79 patients treated with 5-FU and oxaliplatin, showed a higher prevalence of CASH in patients who had neoadjuvant irinotecan-based chemotherapy before liver resection when compared with patients who had no chemotherapy

**Table 1.** Chemotherapy for CRC and associated pathologies.

Pathology	Chemotherapy	Associated morbidities
Steatosis	5-FU	Liver failure
	Irinotecan	Infectious complications
	Oxaliplatin	Bile leak
Steatohepatitis	Irinotecan	Liver failure
SOS	Oxaliplatin	Biliary complications
		Liver failure
		Increased perioperative blood transfusions
Noncirrhotic portal hypertension	Oxaliplatin + 5-FU	Liver failure

CRC, colorectal cancer; 5-FU, 5-fluorouracil; SOS, sinusoidal obstruction syndrome.

(20.2% *versus* 4.4%, $p = 0.001$). In the same study, there was no difference in CASH incidence of patients treated with oxaliplatin-based regimens (6.2% *versus* 4.4%). The patients receiving oxaliplatin were, however, noted to have increased rates of grade 2 or 3 sinusoidal dilation (18.9% *versus* 1.9, $p < 0.001$).[30] A second study compared patients who were treated pre-operatively with 5-FU, irinotecan, and/or oxaliplatin, or no chemotherapy. The degree of CASH was graded utilizing the previously described Brunt system, which grades NASH necroinflammatory features.[31] The irinotecan/oxaliplatin arm was found to have a significantly worse score when compared with the other two groups [1.9 *versus* 1.2 (no chemo) *versus* 1.1 (5-FU); $p = 0.003$].[32] The irinotecan/oxaliplatin arm comprised 14 patients, and only 4 were treated with oxaliplatin; therefore, it was felt that the increase in score was secondary to irinotecan use primarily. However, given the small numbers in this study it is difficult to associate CASH with irinotecan specifically. A meta-analysis also demonstrated that inclusion of irinotecan in the preoperative chemotherapy regimen was associated with a 3.4-fold increase in the risk of steatohepatitis when compared with no chemotherapy, and that one out of two patients treated with irinotecan would likely develop CASH as a result of therapy.[21] The development of irinotecan-induced steatohepatitis has been studied in human hepatocytes, mice treated with irinotecan, and resected liver specimens from irinotecan-treated patients compared with patients not treated with irinotecan. It appears that irinotecan exerted a dose-dependent induction in lipid accumulation

and pro-inflammatory gene expression. Not surprisingly, as steatosis is the generally seen before development of steatohepatitis, some loss of mitochondrial function and reduced expression of carnitine palmitoyltransferase I with induction of ACOX1 was noted. Additionally, there was an increase in oxidative stress and activation of extracellular signal-regulated kinase (ERK).[33] Inhibiting ERK blocked irinotecan-induced pro-inflammatory gene expression while having only a small effect on lipid accumulation. Pretreatment with the tyrosine kinase inhibitor sorafenib significantly reduced ERK activation and the associated inflammatory response without impacting on autophagy or steatosis in irinotecan-treated hepatocytes and murine livers.[33] As such, it is thought that irinotecan induces hepatic steatosis secondary to inflammation *via* ERK activation.[33,34] Additional studies have also shown that the role of the gut microbiota, and that bacterial translocation may participate in the development of CASH (see below).[35] In conclusion, in CRC patients receiving chemotherapy, irinotecan is thought to be responsible for the development of CASH, but the mechanism by which CASH develops is being continually investigated.

SOS is considered the result of severe toxic injury affecting the hepatic sinusoidal endothelial cells. Oxaliplatin-based regimens have been suggested to cause SOS. On histologic evaluation, SOS is characterized by distinctly dilated sinusoids with congestion, and, in extreme cases, it can be associated with perisinusoidal fibrosis and nodular regenerative hyperplasia. Macroscopically, the
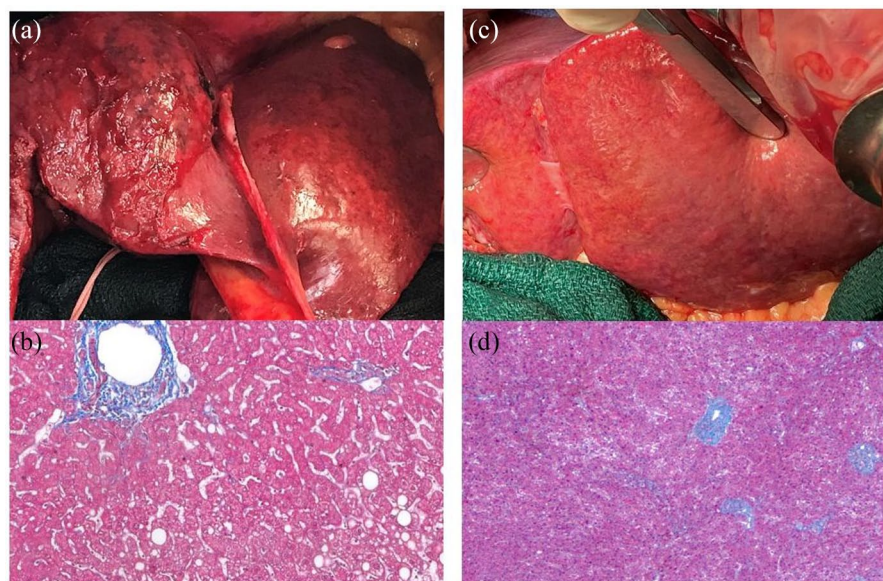
Figure 1. Gross and histologic effects of oxaliplatin. (A) Liver treated with eight cycles of FOLFOX, marbled appearance with blue tones; (B) Liver a histology – mild fat with hepatocyte dropout seen on histology; (C) Liver treated with six cycles of FOLFOX and VEGF inhibitor (Avastin), steatotic appearing; and (D) Liver c histology – minimal fat with patchy nodular regenerative hyperplasia.
FOLFOX, oxaliplatin with 5-FU and leucovorin; 5-FU, 5-fluorouracil; VEGF, vascular endothelial growth factor.

description of a "blue liver" has been used to describe the bluish-red marbled appearance of the liver that results from SOS (Figure 1). The reported incidence of SOS secondary to oxaliplatin is between 8% and 49% (Table 2). There are varying types of sinusoidal changes that can be observed, ranging from congestive sinusoidal dilation in the centrilobular area in 35–40%, perisinusoidal fibrosis in 30%, low grade nodular regenerative changes in 12–20%, and atrophy in liver cell plates.[16,36] The classification of SOS groups patients into mild (less than 1/3 of lobule), moderate (1/3–2/3 of lobule), and severe changes (extending into lobule).[10,37] Recent studies have shown that SOS can impair hepatic reserve, diminish chemotherapy response in patients with liver metastases, compromise liver regeneration post hepatic resection, and may lead to higher morbidity after hepatic resection.[10,12,30,38] Research shows that the molecular pathophysiology of oxaliplatin-induced SOS involves the depolymerization of F-actin in sinusoidal endothelial cells, which results in increased expression of matrix metalloproteinase (MMP)-9 and MMP-2 by sinusoidal endothelial cells.[39] Morphologically, microscopic evaluation revealed that red blood cells penetrated under the sinusoidal endothelial cell barrier and dissected the endothelium off the

extracellular matrix in the space of Disse. Higher MMP activity could have facilitated this process by breaking down the extracellular matrix. Oxaliplatin administration has also been shown to activate hepatic stellate cells, resulting in the deposition of a collagen matrix in the perisinusoidal spaces and centrilobular veins.[10,40,41] In a murine chemotherapy model of FOLFOX-induced SOS, there was evidence of endothelial damage that led to a pro-thrombotic state within the liver. This was associated with upregulation of plasminogen activator 1 (PAI-1) and von Willebrand factor and factor X, which may have contributed to the propagation of liver injury.[21] Additionally, administration of oxaliplatin with 5-FU can result in steatosis and fibrosis by previously described mechanisms, ultimately leading to portal hypertension and liver dysfunction.

Regarding the impact of duration of chemotherapy exposure prior to operative intervention, Karoui *et al.* reported that patients receiving systemic chemotherapy (most of whom were treated with oxaliplatin) were noted to have higher rates of SOS (49% *versus* 13%, $p = 0.005$) and postoperative complications (38% *versus* 13.5%, $p = 0.03$).[42] This was found to be more pronounced in patients who received >6 cycles as

Table 2. Association of oxaliplatin-associated toxicity – sinusoidal dilation.

Study	Pts (n)	Sinusoidal dilation	% of Pts with moderate/severe sinusoidal obstruction	Greater morbidity	Greater mortality
Rubbia-Brandt et al.[10]	43	78%	54%	NA	NA
Vauthey et al.[30]	79	19%	5.4%	No	No
Alioa et al.[38]	52	19%	Not Recorded	Yes	No
Karoui et al.[42]	45	49%	Not Recorded	Yes	No
Pawlik et al.[12]	31	10%	9.7%	No	No
Kandutsch et al.[43]	47	23%	23%	No	No
Mehta et al.[44]	70	61%	8.60%	No	No
Nakano et al.[45]	90	42%	40%	Yes	No
Overman et al.[46]	63	22%	22%	NA	NA

Grade of Sinusoidal Dilation: Grade 2, moderate (centrilobular involvement extending in two-thirds of the lobular area); 3, severe (complete lobular involvement or centrilobular involvement extending to adjacent lobules with bridging congestion).
NA, not available; Pts, patients.

compared with those treated with <6 cycles.[42] Another study demonstrated higher rates of postoperative liver failure in patients receiving >10 cycles of chemotherapy whereas yet another showed no difference in morbidity.[36,47] The impact of chemotherapy on postoperative morbidity and mortality remains controversial, but the changes in liver histology and function have been well described. Currently, the benefits of chemotherapy for CRLM outweigh the risks, but a thorough understanding of potential downstream complications is instrumental in the management of these patients.

Role of the gut microbiome in chemotherapy-induced liver injury

Growing evidence suggests that the gut microbiome likely plays a key role in carcinogenesis, and influences both the efficacy and toxicity of various anticancer agents. The gut and liver communicate *via* the biliary tract, portal vein, and systemic circulation. In the intestine, host and microbes metabolize endogenous as well as exogenous substrates, the products of which translocate to the liver and influence liver functions. Given that the microbiome can affect drug metabolism, pharmacokinetics, and bioavailability, chemotherapeutic agents are likely influenced by the gut microbiome.[48] For example, patients with NAFLD are known to have more small intestinal

bacterial overgrowth and microbial imbalance.[49] Additionally, there is evidence that, for example, oxaliplatin administration may prime myeloid cells to produce ROS.[50] As more research is completed, there is growing body of evidence that the microbiome mediates the host response by facilitating drug efficacy, at times compromising anticancer effects, and may facilitate toxicity.[35,51] This will undoubtedly be an area of continued study and must be considered in the evolution of chemotherapy-mediated liver injury.

Strategies to lower incidence of liver injury due to systemic chemotherapy

Identifying treatments to diminish the degree of chemotherapy-induced liver injury is of paramount importance. Studies have reported that bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor that improves efficacy of systemic chemotherapy in patients with metastatic CRC, may also play a protective role in the development of SOS.[52–54] Ribero *et al.* were the first to evaluate the impact of bevacizumab on nontumorous liver parenchyma.[54] They identified that the incidence of sinusoidal dilation of any grade was lower in patients treated with bevacizumab compared with those patients not treated with bevacizumab (27.4% *versus* 53.5%; $p = 0.006$).[54] Subsequent studies have also reported decreased rates of development and progression of SOS

from treatment with bevacizumab without explaining a mechanism.[55–57] Given that oxaliplatin appeared to contribute to liver pro-thrombotic state with upregulation of various thrombogenic factors, administration of bevacizumab may, in fact, reduce liver injury in this fashion.[58] There are, however, other studies that report the negative impact of bevacizumab secondary to compromise of liver regenerative ability. Additionally, in animal studies, anti-VEGF administration appeared to enhance MMP-9 production, which, in turn, caused higher rates of SOS.[39,59] Thus, the data available regarding the liver protective effects of anti-VEGF therapy are limited, and no clear conclusion regarding the impact of anti-VEGF therapy on SOS is possible.

Another agent for consideration is S-adenosyl-methionine (SAMe). SAMe is the primary biological methyl donor, and is synthesized by the methionine adenosyltransferase (MAT) family of proteins. It plays an important role in a variety of functions, including trans-methylation reactions and regulation of cellular metabolism, cell growth, and apoptosis.[60] Diseased liver has been identified to have low levels of SAMe, which has been attributed to decreased expression of methionine adenosyl transferase 1A (MAT1A), an enzyme responsible for hepatic SAMe biosynthesis.[60,61] SAMe is also a precursor for glutathione (GSH), and treatment with SAMe has been shown to raise hepatic GSH levels in patients with cirrhosis. It has been shown that patients with liver dysfunction have decreased levels of SAMe and MAT1A, and decreased glutathione. It has also been found to reduce lipopolysaccharide-induced liver injury through reduction in tumor necrosis factor alpha (TNF-α) expression, and to block transforming growth factor beta (TGF-β) mediated ERK activation in hepatic stellate cells (HSC), which may contribute to its anti-fibrogenic effects.[62] A few studies, both observational and retrospective, have demonstrated that SAMe may have a protective effect in chemotherapy-induced liver injury. Patients who received SAMe were noted to have lower serum concentrations of aspartate transaminase and alanine transaminase, and this persisted throughout their course of SAMe treatment.[63–65] Additional research is required, but certainly preliminary data suggests that SAMe likely has a protective effect for chemotherapy-induced liver injury.

Conclusion

Over the past few decades, awareness of the various hepatic toxicities of chemotherapy has increased dramatically. The associations between chemotherapy and steatosis, irinotecan and CASH and oxaliplatin and SOS have been evaluated and established. There is controversial data regarding association of chemotherapy and degree of post-operative morbidity, but there is clearly a correlation suggesting that there is likely an impact. Detection of chemotherapy-induced liver injuries further emphasizes the need for individualized, multidisciplinary care. Patients with CRC and especially CRLM should be evaluated by experienced medical and surgical oncologists before initiating therapy to avoid excessive and unnecessary treatment. Similar response rates with FOLFOX and FOLFIRI balanced against the unique chemotherapy-mediated liver toxicities associated with each regimen should be considered when planning therapy with first-line *versus* second-line treatments for operative CRLM patients. Finally, additional strategies for prevention of liver injury must be identified given the prevalence of CRC and the improved survival of diagnosed patients.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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