Chemotherapy-Associated Hepatotoxicities

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KEYWORDS

• Liver injury • Chemotherapy • Hepatectomy • Steatosis • Steatohepatitis
• Sinusoidal obstruction syndrome

KEY POINTS

- Steatosis is most commonly associated with irinotecan and 5-fluorouracil, whereas sinusoidal obstruction syndrome is more frequently noted with oxaliplatin. Steatohepatitis has only been linked to irinotecan.
- Most investigators agree that presence of steatosis has little impact on surgical outcomes, whereas steatohepatitis leads to increased mortality.
- Sinusoidal obstruction syndrome can predispose patients to increased blood loss, earlier disease recurrence, and decreased overall survival.
- Duration of preoperative chemotherapy and time interval after completion of chemotherapy before surgery can be optimized to reduce liver toxicities.

OVERVIEW

The number of chemotherapy options and combination regimens for a multitude of malignancies has vastly increased in the last few decades. An unfortunate consequence of using increasingly effective systemic cytotoxic therapies before hepatectomy is their off-target effects that result in concurrent damage to normal tissues. The mechanisms and readouts for level of host tissue damage are increasingly understood. Hepatic toxicities are notable, as they can not only impact a patient's overall health and recovery from surgery but also impair the regenerative capacity that is the basis of potentially curative resections of the liver, a common site for metastatic disease to present. Surgeons in particular must account for chemotherapy-associated liver injuries when considering liver resection for metastasectomy in planning safe surgery.

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CATEGORIES OF HEPATOTOXICITY

Two major categories of hepatic tissue damage commonly occur as a consequence of chemotherapy. The first is similar to nonalcoholic fatty liver disease and often referred to as *CASH*, for chemotherapy-associated steatohepatitis.[1] This form of nonalcoholic fatty liver disease can be further divided into steatosis and steatohepatitis. Nonalcoholic fatty liver disease is classified as a greater than 5% infiltration of hepatocytes by triglycerides in patients without significant alcohol consumption.[2] In steatosis, lipid accumulates to abundance in hepatocytes, whereas steatohepatitis indicates concurrent inflammatory changes and ballooning degeneration of the hepatocytes.[2] These fatty liver diseases lead to the classic fatty or yellow liver that can be noted on gross examination owing to a yellowed (or frequently pink) hue of the liver parenchyma (**Fig. 1**A). A scoring system for these fatty liver changes has been developed by Kleiner and colleagues and termed the Nonalcoholic Fatty Liver Disease Activity Score (**Table 1**).[3] This scoring system includes 14 histologic categories. Three of those—degree of steatosis, lobular inflammation, and hepatocellular ballooning—are given quantitative scores with a range from 0 to 8. The sum of these unweighted scores is used to classify histologic findings as steatosis versus steatohepatitis with good reproducibility among evaluators. Scores greater than 5 are consistent with steatohepatitis, whereas scores less than 3 are considered not steatohepatitis.[3] Patients with steatohepatitis are at risk for progressive disease culminating in fibrosis and possible cirrhosis and have a 10-fold increased risk of death from liver disease.[2]

The second category results from injury to the sinusoids causing venous congestion and blue liver, a term coined because of its macroscopic appearance (**Fig. 1**B). Endothelial cells in the sinusoids become damaged leading to initiation of the coagulation cascade within the subendothelial space of Disse and ultimately sinusoidal obstruction as fibrotic changes occur to the central venules.[4] Sinusoidal injury can also be scored based on a system devised by Rubbia-Brandt and colleagues[5] with grades 0 to 3 (**Table 2**). The range of sinusoidal injury can go from mild changes such as sinusoidal dilation progressing on the extreme end to veno-occlusive changes with regenerative nodular hyperplasia.[5] Severe chemotherapy-associated veno-occlusive disease can have the behavior and radiologic appearance of the Budd-Chiari syndrome.[5]

SCOPE OF THE PROBLEM

Although primary liver cancers are common worldwide, metastatic disease to the liver is far more abundant in the United States. The most common primary site for

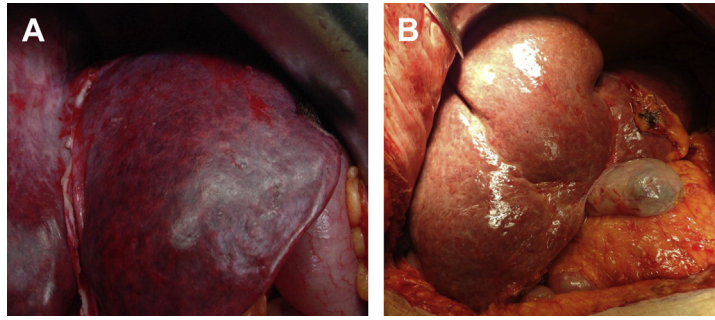


Fig. 1. (*A*) Blue liver consistent with sinusoidal obstruction syndrome. (*B*) Yellow liver with steatosis and some nodularity consistent with fibrotic changes.

Table 1
Nonalcoholic fatty liver disease activity scoring system

	Scoring Criteria
Steatosis	0: <5% Fatty infiltration 1: 5%–33% 2: 33%–66% 3: >66%
Lobular inflammation	0: None 1: <2 Foci/200x field 2: 2–4 Foci/200x field 3: > 4 Foci/200x field
Hepatocyte ballooning	0: None 1: Minimal ballooning 2: Prominent ballooning

Scores from 0 to 2 are not consistent with steatohepatitis. Scores from 5 to 8 correlate with a diagnosis of steatohepatitis.

Data from Kleiner DE, Brunt EM, Van Natta M, et al. Design and validation of a histologic scoring system for nonalcoholic fatty liver disease. Hepatology 2005;41(6):1319.

metastatic lesions to the liver is from colorectal cancers. More than 136,000 new cases of colon and rectal cancer were diagnosed in the United States last year, making it the second most common cancer in men and third most common in women.[6] Approximately 25% of these patients present at initial diagnosis with synchronous liver metastases, and up to 60% of colorectal cancer patients will have metastatic disease to the liver during the course of their disease.[7] The treatment and prognosis for these patients has significantly improved in the last 20 years in large part because of improvements in systemic therapy and a better understanding of the surgical management of liver metastases. We have learned that with colorectal cancer patients that have liver-only metastases, long-term survival and often cure can be achieved if complete surgical resection is possible.[8] These patients will frequently get chemotherapy either in the preoperative setting or adjuvantly. Use of neoadjuvant chemotherapy can convert disease initially deemed unresectable to resectable disease 10% to 15% of the time.[9] These patients are also found to have similar survival outcomes to those who were upfront surgical candidates.[10] As a result of these advancements in the treatment regimen for patients with hepatic metastases from colorectal cancer, a large number of patients receive systemic chemotherapy that can be potentially damaging to the liver.

Table 2
Sinusoidal obstruction syndrome grading system

Grade 0	No sinusoidal dilation identified
Grade 1	(Mild) Sinusoidal dilation of up to 1/3 of the lobular surface
Grade 2	(Moderate) Sinusoidal dilation of up to 2/3 of the lobular surface
Grade 3	(Severe) Sinusoidal dilation throughout

Grading system for sinusoidal obstruction syndrome of the liver.

Adapted from Rubbia-Brandt L, Audard V, Sartoretti P, et al. Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. Ann Oncol 2004;15(3):461.

Paramount to the advancement of our treatment of colorectal cancers has been the development of 3 primary cytotoxic chemotherapy agents, 5-Fluorouracil (5-FU), oxaliplatin, and irinotecan. Use of these agents has now been linked to predictable hepatotoxicities including steatosis, steatohepatitis, and sinusoidal obstructive syndrome. Irinotecan and 5-FU are more associated with steatosis.[11] Steatohepatitis has only been linked to irinotecan,[12] whereas oxaliplatin regimens can result in sinusoidal injuries leading to sinusoidal obstruction syndrome.[11–13]

In addition, patients with elevated body mass index, type 2 diabetes mellitus, or metabolic syndrome have an increased risk for steatosis irrespective of chemotherapy. Up to one-third of the population is thought to likely have some degree of nonalcoholic fatty liver disease caused by the worldwide obesity epidemic.[2] Although mild steatosis is thought to be relatively benign, it is thought that patients with baseline nonalcoholic fatty liver disease are at higher risk for chemotherapy-associated liver injuries than those without.

MECHANISMS

The basic underlying principle for hepatotoxicities from cytotoxic chemotherapies is related to the development of reactive oxygen species leading to cellular damage and apoptosis pathways. It is thought that livers with preexisting nonalcoholic steatosis changes are most susceptible to further damage from use of chemotherapy. 5-FU and Irinotecan specifically are thought to affect mitochondrial membranes allowing for an increase in reactive oxygen species and setting off a cascade of events leading to lipid peroxidation, fibrosis, and cell death.[14,15] Sinusoidal injury is also thought to result from reactive oxygen species. Once these endothelial cells are injured, the coagulation cascade is activated and can lead to sinusoidal obstruction.[5]

IDENTIFICATION OF LIVER INJURY

Although definitive diagnosis of any of these chemotherapy-associated hepatotoxicities requires histologic examination of tissue, it is often helpful to be able to predict or identify these patients, especially in a preoperative setting.

Nonalcoholic fatty liver disease is usually asymptomatic; thus, clinical suspicion (such as identifying overweight, diabetic, and chemotherapy-treated patients) is necessary to diagnose this disease. Laboratory abnormalities are insensitive but an increase in alanine aminotransferase greater than aspartate aminotransferase is frequently present in nonalcoholic fatty liver disease.[2] With elevation of liver transaminases, other causes of liver injury including but not limited to alcohol use, hepatitis, and autoimmune hepatitis should be ruled out.[2] Steatohepatitis can progress to fibrosis and ultimately cirrhosis of the liver. In these cases, thrombocytopenia that is not corrected after cessation of chemotherapy is often noted.[1] In sinusoidal obstruction syndrome, rather than elevated transaminases, a picture of cholestasis with elevations in alkaline phosphatase or γ-glutamyl transpeptidase is seen[13] (**Table 3**).

Ultrasound scan, computed tomography (CT) and MRI are all commonly used imaging modalities to help identify liver injuries. Ultrasound scan is inexpensive but user dependent and not as sensitive for early steatosis.[2] CT imaging, which is often obtained to look for metastatic disease, can identify steatosis with low attenuation of liver tissue on nonenhanced images with Hounsfield unit values of less than 40 compared with a normal range of 50 to 57.[1,2] Another metric that is often used is an attenuation ratio of liver to spleen greater than 1.1 that is predictive of more than 30% steatosis.[2] Findings of splenomegaly are suggestive of more advanced liver disease such as cirrhosis[1] (**Fig. 2**). MRI, the most expensive, is thought to be the most accurate at

Table 3
Characteristics of chemotherapy-associated liver injury categories

	Steatosis	Steatohepatitis	Sinusoidal Obstruction
Mechanism	Reactive oxygen species causing cellular damage and apoptosis. Mitochondrial membrane damage, lipid peroxidation, fibrosis, cellular death.	Reactive oxygen species causing cellular damage and apoptosis. Mitochondrial membrane damage, lipid peroxidation, fibrosis, cellular death.	Reactive oxygen species causing damage to endothelial cells, extravasation of red blood cells into perisinusoidal spaces, venous outflow obstruction and subsequent dilation of sinusoids.
Laboratory abnormalities	Increased ALT > AST	Increased ALT > AST	Increased Alk Phos or gGT
Gross appearance	Yellow, fatty	Yellow, fatty	Blue, congested
Pathology	Greater that 5% triglyceride infiltration into hepatocytes	Steatosis changes plus lobular inflammation, hepatocellular ballooning, fibrosis	Sinusoidal dilation, fibrotic changes to central venules, perisinusoidal fibrosis, possible regenerative nodular hyperplasia

Abbreviations: Alk Phos, Alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; gGT, Gamma-glutamyl transpeptidase.

predicting steatosis and is proposed by some as a method for identifying sinusoidal injury.[2] A study by Cho and colleagues[16] in 2008 compared noncontrast CT, contrast-enhanced CT, and MRI for detection of steatosis and compared these findings with histologic analysis of tissues. In their study, sensitivity and specificity for each modality (noncontrast CT, contrast-enhanced CT, MRI) were 33% and 100%, 50% and 83%, and 88% and 63%, respectively. They concluded that significant steatosis could be identified on noncontrast CT, but a CT read as normal could not exclude the diagnosis. MRI was good for exclusion of steatosis but had poor ability to identify nonalcoholic fatty liver changes.[16]

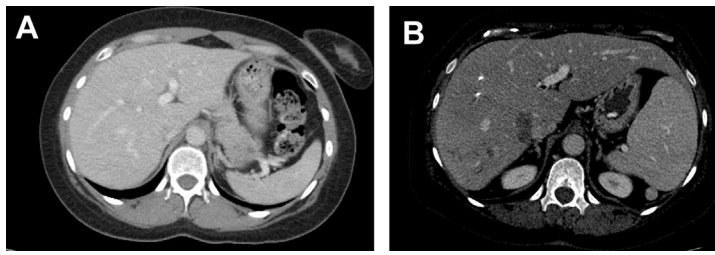


Fig. 2. (*A*) CT scan axial image of normal liver without evidence of chemotherapy-associated hepatotoxicities. (*B*) CT scan axial image of a fatty liver consistent with steatosis. Note the low attenuation of the liver relative to the spleen and associated splenomegaly suggesting possible fibrosis or cirrhotic changes.

The current gold standard would include laparoscopic evaluation of the liver to assess macroscopic changes and tissue biopsy for pathologic review of uninvolved liver parenchyma. Despite this finding, because of the invasive nature of laparoscopy and biopsy, they are often not performed before the definitive operation.

IMPACT OF CHEMOTHERAPY-ASSOCIATED HEPATOTOXICITIES

In general, many surgeons believe chemotherapy-associated liver injuries are deleterious to surgical outcomes related to liver resections. The literature has not demonstrated a true consensus on this common perception. Numerous studies looked at the impact of chemotherapy-induced liver injury, and key studies are discussed in this review.

A study by Vigano and colleagues[17] in 2013 looked at 323 patients over a span of 13 years who were undergoing liver resection for metastatic colorectal cancers. All patients were treated preoperatively with either oxaliplatin or irinotecan-based chemotherapy regimens. Grade 2 or 3 sinusoidal obstruction was noted in 38.4% (all grades 64.1%) of patients and grade 2 or 3 steatosis in 22.6%. Steatohepatitis was seen in 9.3% of the patients. They noted that patients who had moderate or severe sinusoidal obstruction had less of a pathologic response of the tumor to chemotherapy. Although tumor response to chemotherapy was prognostically significant, chemotherapy-associated liver injuries did not have a negative impact on long-term survival. Steatosis was actually noted to have a protective survival impact that has also been shown in other studies.[17,18]

Reddy and colleagues[19] performed a retrospective study looking at hepatic steatosis and compared the likelihood of progression to advanced hepatic fibrosis in patients previously treated with chemotherapy versus those who had never received chemotherapy. They found on multivariable analysis that chemotherapy treatment, especially 5-FU and irinotecan, was a negative predictor for having a low probability of finding advanced fibrosis in patients with steatosis. They suggest that chemotherapy-treated patients with steatosis at least 6 months after their last treatment should be closely evaluated for development of progressive fibrosis of the liver.[19]

Additional studies looked at perioperative morbidity and mortality as it relates to chemotherapy-associated liver injury (**Table 4**). In a 2006 study by Vauthey and colleagues,[12] 406 patients who underwent hepatectomy for colorectal cancer metastases were reviewed retrospectively. More than 60% of the patients had received preoperative chemotherapy (n = 248), and common agents included 5-FU, oxaliplatin, and irinotecan. Approximately 9% of patients had steatosis, 8% had steatohepatitis, and 5% had sinusoidal changes. Consistent with many other studies, oxaliplatin was associated with sinusoidal obstruction, whereas irinotecan was independently associated with steatohepatitis. They noted that patients with steatohepatitis had a significantly increased risk of 90-day mortality at 14.7% compared with 1.6% in those without.[12]

Pawlik and colleagues[11] similarly looked at 212 patients retrospectively in 2007 that had hepatic resections for metastatic colorectal cancer. They similarly found an association of sinusoidal injury with oxaliplatin use, and steatosis of nearly 30% was associated with irinotecan use. In their study, only 3 patients were identified to have steatohepatitis, 2 of whom had received irinotecan. They found no statistical difference in perioperative morbidity rates or 60-day mortality when comparing patients who received preoperative chemotherapy with those who did not.

A recent European study by Parkin and colleagues[20] identified 4329 patients through the LiverMetSurvey that had first-time liver resections after neoadjuvant

Table 4
Perioperative morbidity and mortality related to chemotherapy-associated liver injury

Study, Year	Number of Patients Treated with Chemotherapy	Agents Used (% Patients)	Hepatotoxicities (% of Total)	Chemotherapy Agent and Toxicity (Odds Ratio or % of Treated Patients)	Conclusions
Vauthey et al,[12] 2006	248	5-FU alone (15.5%) 5-FU + irinotecan (23.1%) 5-FU + oxaliplatin (19.5%)	Steatosis (8.9%) Steatohepatitis (8.4%) Sinusoidal dilation (5.4%)	Oxaliplatin–sinusoidal dilation (OR, 8.3; *P*<.001) Irinotecan–steatohepatitis (OR, 5.4; *P*<.001)	Steatohepatitis– increased 90-d mortality (OR, 10.5; *P* = .001)
Pawlik et al,[11] 2007	153	5-FU alone (31.6%) 5-FU + irinotecan (25.9%) 5-FU + oxaliplatin (14.6%)	Steatosis (19.6%) Steatohepatitis (2.0%) Sinusoidal dilation (4.6%)	Irinotecan–steatosis (27.3%) Oxaliplatin–sinusoidal dilation (9.7%)	Unchanged perioperative complication rate and 60-d mortality between chemotherapy and no chemotherapy groups
Parkin et al,[20] 2014	4329	5-FU (76%) Irinotecan (29.2%) Oxaliplatin (55.6%) Capecitabine (15%) Bevacizumab (23.4%) Cetuximab (7.1%)	NR	NR	No difference in 5-y OS or CSS in patients with steatosis vs those without
Wolf et al,[21] 2013	250	Oxaliplatin (66.4%) Irinotecan (43.6%) Bevacizumab (29.2%)	Steatosis (38%) Steatohepatitis (6%) Sinusoidal dilation (10%)	Irinotecan–steatosis (46%; *P*<.01), steatohepatitis (8%; *P* = .01)	No association between early postoperative mortality, steatohepatitis or preoperative chemotherapy
Tamandl et al,[13] 2011	161	FOLFOX/XELOX (52.2%) FOLFOX/XELOX + Bevacizumab (30%) FOLFIRI or FOLFOX conversion to FOLFIRI (16.1%)	Sinusoidal dilation grade 2–3 (27%)	FOLFOX or XELOX–sinusoidal dilation grade 2–3 (18.1%; *P* = .011)	Sinusoidal obstruction syndrome decreases recurrence-free survival and overall survival. No increase in perioperative morbidity.

Abbreviations: CSS, cancer specific survival; FOLFIRI, Folinic acid (leucovorin), 5-Fluorouracil, irinotecan; FOLFOX, Folinic acid (leucovorin), 5-Fluorouracil, oxaliplatin; NR, not reported; OR, odds ratio; OS, overall survival; XELOX, capecitabine, oxaliplatin.
Data from Refs.[11–13,20,21]

chemotherapy. This study compared 90-day mortality, 5-year overall survival, and 5-year cancer specific survival based on 3 liver histology groups that included normal liver, steatosis and other. They found no statistically significant difference in any of their survival endpoints across the 3 groups, suggesting that steatosis should not compromise oncologic outcomes or perioperative mortality in this patient population.

In 2013, Wolf and colleagues[21] reviewed 384 patients who had pathologic tissue available for review after resection of metastatic colorectal metastases to the liver. In this retrospective study, 65% of patients had preoperative chemotherapy for a median of 24 weeks. They found chemotherapy to be protective against major perioperative morbidity and mortality.

In contrast, Tamandl and colleagues[13] were able to identify a worsened outcome in patients with sinusoidal obstruction after preoperative chemotherapy before hepatic metastasectomy for colorectal cancer. In their study, 18% of patients receiving oxaliplatin-based chemotherapy regimens subsequently had grade 2 or 3 sinusoidal obstruction. They were able to show in their study that these patients had earlier recurrence of their disease and decreased overall survival; however, there was no increase in perioperative morbidity.

MANAGEMENT OF CHEMOTHERAPY-ASSOCIATED HEPATOTOXICITIES

With a greater understanding of the specific agents that cause chemotherapy-associated liver injuries, efforts have been made to minimize the extent of damage that is induced. Many chemotherapy-associated liver injuries are noted to be reversible, especially in earlier stages if surgery is delayed after completion of chemotherapy.[4,22] Duration of therapy is thought to correlate with the extent of liver damage and have an impact on perioperative outcomes. Aloia and colleagues[23] demonstrated that patients receiving more than 12 cycles of preoperative chemotherapy were more likely to require reoperation (11% vs 0%) and to have a longer hospital length of stay (15 days vs 11). As a result of this and other studies, some suggest stopping chemotherapy in the preoperative setting once metastatic lesions are resectable rather than treating to maximal response. Others suggest 4 months as the optimal duration of treatment to obtain the greatest tumor response balanced with minimizing liver toxicity.[12]

Other investigators looked at the interval between the last dose of chemotherapy and date of surgery as a way to minimize operative complications that could be related to treatment-induced liver injuries. Numerous studies show a reduction in chemotherapy-associated liver injuries with longer time intervals after chemotherapy; however, this also must be balanced against the risk of regrowth of the tumor during that treatment-free period. Many surgeons consider 4 to 6 weeks the appropriate interval, and these authors recommend waiting 5 weeks from the last chemotherapy treatment before taking a patient to surgery for hepatic resection.[24,25]

A proper assessment of the estimated functional liver remnant is important before taking a patient for large-volume liver resections. In patients with suspected chemotherapy-induced liver injuries, most surgeons agree that a future liver remnant of at least 30% is necessary to minimize risk for postoperative hepatic failure.[26] This is compared with 20% to 25% in patients with healthy liver tissue. Methods to optimize the future liver remnant including portal vein embolization are beyond the scope of this report and are discussed elsewhere.

Combined ablation and resection is a technique that can be used to spare liver parenchyma in patients with extensive liver disease that would previously be considered unresectable. This technique was evaluated in a multicenter study to look at

complication rates and survival outcomes.[27] Combined ablation and resection was performed on 288 patients across 4 centers, most with synchronous and bilateral colorectal liver metastases. Median hepatic recurrence-free survival in these patients was 14 months. Complications occurred in 35% of patients and were an independent risk factor for overall survival. Five-year overall survival rate was 45% in patients without and 25.6% for those with complications. The 30-day mortality rate was low at 1%.

Lastly, some investigators noted that use of bevacizumab may have a protective effect against sinusoidal injuries to the liver if used in the preoperative setting. Although the percentage of patients with grade 2 or 3 sinusoidal injuries was reduced, the surgical complication rate was not significantly changed.[28,29]

SUMMARY

Hepatotoxic side effects from chemotherapy remain a major hurdle for the treatment of numerous malignancies. These effects have become better characterized over the last decade and include a spectrum of nonalcoholic fatty liver disease including steatosis and steatohepatitis (chemotherapy-associated steatohepatitis) and sinusoidal injuries. The incidence of these liver injuries is predictable based on chemotherapy regimen, and their presence can complicate attempts for curative surgical resection of liver metastases. Oxaliplatin-based chemotherapy regimens are more commonly associated with sinusoidal obstructive liver injury, whereas irinotecan and 5-FU are more frequently associated with steatosis. Steatohepatitis has only been linked to irinotecan. Increased awareness and understanding of these chemotherapy-induced side effects has allowed medical oncologists and liver surgeons to develop treatment plans that help minimize risk for severe liver injury and to appropriately plan preoperatively to avoid serious complications. Further work remains to be done to increase our knowledge of the mechanisms for these injuries, to identify those patients at highest risk, and to help prevent these side effects entirely in the future.

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