

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. 1A). 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. 1B). 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 colleagues⁵ 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

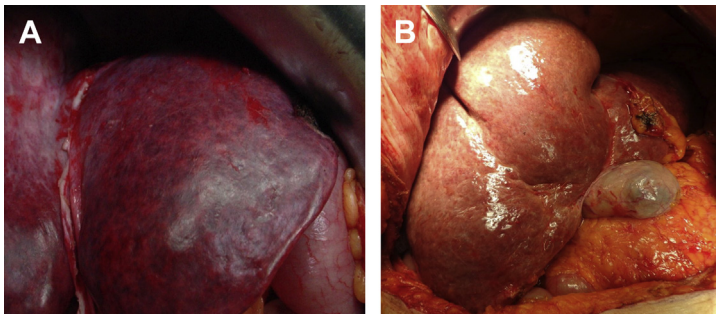


Fig. 1. (A) Blue liver consistent with sinusoidal obstruction syndrome. (B) Yellow liver with steatosis and some nodularity consistent with fibrotic changes.

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