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Review

Imaging of hepatic toxicity of systemic therapy in a tertiary cancer centre: chemotherapy, haematopoietic stem cell transplantation, molecular targeted therapies, and immune checkpoint inhibitors

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The purpose of this review is to familiarise radiologists with the spectrum of hepatic toxicity seen in the oncology setting, in view of the different systemic therapies used in cancer patients. Drug-induced liver injury can manifest in various forms, and anti-neoplastic agents are associated with different types of hepatotoxicity. Although chemotherapy-induced liver injury can present as hepatitis, steatosis, sinusoidal obstruction syndrome, and chronic parenchymal damages, molecular targeted therapy-associated liver toxicity ranges from mild liver function test elevation to fulminant life-threatening acute liver failure. The recent arrival of immune checkpoint inhibitors in oncology has introduced a new range of immune-related adverse events, with differing mechanisms of liver toxicity and varied imaging presentation of liver injury. High-dose chemotherapy regimens for haematopoietic stem cell transplantation are associated with sinusoidal obstruction syndrome. Management of hepatic toxicity depends on the clinical scenario, the drug in use, and the severity of the findings. In this article, we will (1) present the most common types of oncological drugs associated with hepatic toxicity and associated liver injuries; (2) illustrate imaging findings of hepatic toxicities and the possible differential diagnosis; and (3) provide a guide for management of these conditions.

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Introduction

The liver is a prime target organ of interest in oncology for multiple reasons: the high prevalence of primary and secondary liver malignancies; the frequency of hepatic metastasectomy and locoregional liver treatments that may reduce functional hepatic reserve; and finally, the damage

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caused by chemotherapy or other drugs.[1,2] Although improved early detection of liver metastases, better understanding of risk factors for primary liver cancer, and the advent of new surgical and locoregional treatments for cancer involving the liver have resulted in declining mortality from primary and secondary liver cancer in recent years, little has changed for drug-induced liver toxicity. The frequent use of multi-drug regimens, the longer duration of systemic therapies due to increased survival, and lastly, the advent of new treatments for cancer in recent years have increased the potential for drug-induced liver injury (DILI).[1,3,4]

The first reported case of chemotherapy-induced liver toxicity dates back to the early 1950s, and in the past years, efforts to identify, categorise, and define management of DILI associated with chemotherapy were made.[4–7] With the advent of newer oncological drugs, the molecular targeted therapies (MTT) and, more recently, the immune-checkpoint inhibitors, the definition, identification, and management of liver toxicity associated with these drugs is still evolving and continuously shifting as new drugs are developed.[8–10]

Regardless of cause of injury, DILI can manifest as symptoms of abdominal discomfort, examination or imaging findings of hepatomegaly, or laboratory findings of elevated liver function tests (LFTs).[5,11] Thus, symptoms indicative of possible DILI often pose a diagnostic dilemma for the oncologist, as symptoms and signs of liver injury may also be unrelated to chemotherapy. It is of utmost importance for the radiologist to recognise the different patterns of DILI and have a strong working knowledge of specific causative drugs used in different clinical settings, in order to advise on appropriate management. In this article, we will begin with a brief discussion on mechanisms and types of DILI, in view of the different drugs and possible clinical scenarios encountered in oncology. We will illustrate the multimodality imaging patterns of DILI and provide a framework for potential management.

Mechanisms of DILI

DILI is a potential complication of most cancer therapies, because the liver is central to the metabolic clearance of virtually all drugs.[12] DILI can occur secondary to toxicity to hepatocyte and biliary ducts, or indirectly due to either alteration of lipid metabolism or damage to the hepatic vascular network.[13,14] Direct toxicity is common as all drugs are carried to the liver through either the systemic or portal circulations following absorption by the gastrointestinal tract; these drugs are subsequently biotransformed through the cytochrome P-450 enzyme system and other oxidative mechanisms.[15] The end result of drug toxicity is injury to the hepatocytes in the form of mild to severe hepatitis and potential evolution to cirrhosis and fibrosis. Indirect toxicity occurs via altered lipid metabolism, which leads to deposition of fat within the liver, resulting in steatosis or steatohepatitis.[14] Finally, drug-induced vascular changes may lead to liver injury in the form of sinusoid obstructive syndrome (SOS), portal vein thrombosis, and peliosis hepatis.[13]

Types of DILIs

Table 1 shows common chemotherapy agents currently in use and associated liver toxicities. DILI can be either acute or chronic, the latter defined as persistent liver injury >1 year after the initial injury.[16] Acute liver toxicity can manifest as hepatitis, steatosis or steatohepatitis, sinusoidal obstruction syndrome (SOS), or portal vein thrombosis.[5,17,18] Chronic liver toxicity can manifest as steatosis, cirrhosis, nodular regenerative hyperplasia (NRH), or peliosis hepatis.[13] Both acute and chronic liver toxicity can be seen with varying severity, and different types of injury can overlap and coexist, due to the frequent use of multidrug regimens.[5,18] Finally, as will be shown in the last section various conditions may mimic DILI.[5,17,19]

Hepatitis

Drug-induced hepatitis can be categorised histologically into three forms: hepatocellular, cholestatic, or mixed.[20] Distinguishing between the three forms is often not

Table 1
Liver toxicities of cancer therapy.

Type of systemic treatment	Drug-induced liver toxicity
Conventional chemotherapy	
Methotrexate	Hepatic steatosis, NRH, cirrhosis, hepatitis
5-FU	Hepatic steatosis, portal vein thrombosis, hepatitis (intra-arterially)
Vincristine, actinomycin D, and cyclophosphamide	SOS, NRH (cyclophosphamide), hepatitis (cyclophosphamide)
Busulfan	Portal vein thrombosis
L-Asparaginase	Portal vein thrombosis, hepatitis
Gemcitabine	HCV, HBV/HCV reactivation, pseudocirrhosis
Oxaliplatin	SOS, NRH
Paclitaxel and docetaxel	Hepatitis
Cysplatin	Hepatitis
6-Thioguanine	Peliosis hepatis
Tyrosine kinase inhibitor	
Imatinib	Hepatitis
VEGF inhibitor	
Sunitinib	Hepatitis
Pazopanib	Hepatitis
Regorafenib	Hepatitis
EGFR inhibitor	
Erlotinib, gefitinib	Hepatitis
Immune checkpoint inhibitors	
Ipilimumab	Hepatitis
Pembrolizumab	Hepatitis
Nivolumab	Hepatitis
Hormones	
Megestrol acetate/ medroxyprogesterone acetate	Asymptomatic LFTs elevation, jaundice
Tamoxifen	Hepatic steatosis, peliosis hepatis
Anastrozole	Hepatic steatosis
Anti-CD monoclonal antibodies	
Rituximab	HBV/HCV reactivation
Alemtuzumab	HBV/HCV reactivation

NRH, nodular regenerative hyperplasia; SOS, sinusoidal obstruction syndrome; LFTs, liver function tests; VEGF, vascular endothelial growth factor; EGFR, epithelial growth factor receptor; CD, cluster of differentiation.

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