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Liver Injury with Cancer Chemotherapy

– Importance of the Product Label in Risk Stratification

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Cytotoxic chemotherapy is frequently associated with serum aminotransferase elevations that are self-limited and that may subside with continued therapy. However, rare occurrences of jaundice and liver failure have been reported in association with many of these drugs.

Hepatotoxicity identified during clinical development (instead of post-marketing data) is often the basis for the liver toxicity information in the labels for oncology drugs.

Generally, the evidence of potential liver injury is consistent with hepatotoxicity information in the EU Summary of Product Characteristics (SmPC) and U.S. Product Information (PI). However, there is a lack of harmonization regarding location, format, and details of information on hepatotoxicity. Although guidance on liver monitoring is generally mentioned; time to onset of Drug-induced liver injury (DILI), dose modification tables, biochemical profile, or re-challenge information are not always provided.

It is recommended to standardize the information obtained during drug development relating to liver toxicity (time of onset, pattern of injury) and to harmonize the location (sections within the label), format, and level of detail (e.g., monitoring schedule, dose modification table) in the product label.

For combination drugs, the information on liver toxicity of individual drugs (i.e., mechanism, time of onset, pattern of injury) should be used for assessing overlapping liver toxicities.

In oncology clinical trials, the NCI-CTCAE grading system is generally used for grading the severity of liver test abnormalities for suspected DILI cases, and risk management actions are recommended in the product labels based on these severity grades.

Standard serum liver testing should be performed in all oncology patients prior to, during and after chemotherapy, immunotherapy or new treatments that cause liver injury.

Pre-treatment analysis for hepatic metastases with CT or MRI imaging is recommended in all oncology patients who are at increased risk for hepatic spread of tumor, prior to administration of potentially hepatotoxic chemotherapy or immunotherapy.

It is important to understand the pattern of hepatotoxicity with standard chemotherapeutic drugs and the newer class of immunotherapies.

I) Standard Chemotherapeutic Drugs

Some level of hepatotoxicity as well as toxicity to other organs is generally associated with almost all anticancer drugs. With standard chemotherapeutic drugs, the hepatotoxicity is generally direct and dose-dependent; however, with many drugs, serious liver injury may also be due to idiosyncratic mechanisms. Further, hepatotoxicity may manifest in a variety of abnormal histological forms and clinicopathological phenotypes (few examples are mentioned in the Figure below).

Mechanism of Hepatotoxicity with Anti-cancer Drugs

Type	Mechanism(s) of hepatotoxicity (known or suspected)	Examples of associated drugs	Liver injury phenotype
Direct	Alkylation of DNA leads to damage to small blood vessels in the liver	Busulfan (when given for prolonged periods)	Nodular regenerative hyperplasia (NRH)
	Inhibition of methionine synthesis leading to endoplasmic reticulum (ER) stress & activation of stellate cells by excess of homocysteine	Methotrexate	Steatohepatitis, fibrosis, cirrhosis
Indirect	Estrogenic effects on fat metabolism in the liver	Tamoxifen	Fatty liver and steatohepatits
	Secondary to effects on gastrointestinal motility, gut microbiome and bile acid levels	Octreotide	Acute liver injury
Idiosyncratic	Unclear	Temozolomide, cyclophosphamide, melphalan, chlorambucil, azathioprine, tamoxifen	Acute liver injury (mostly cholestatic)

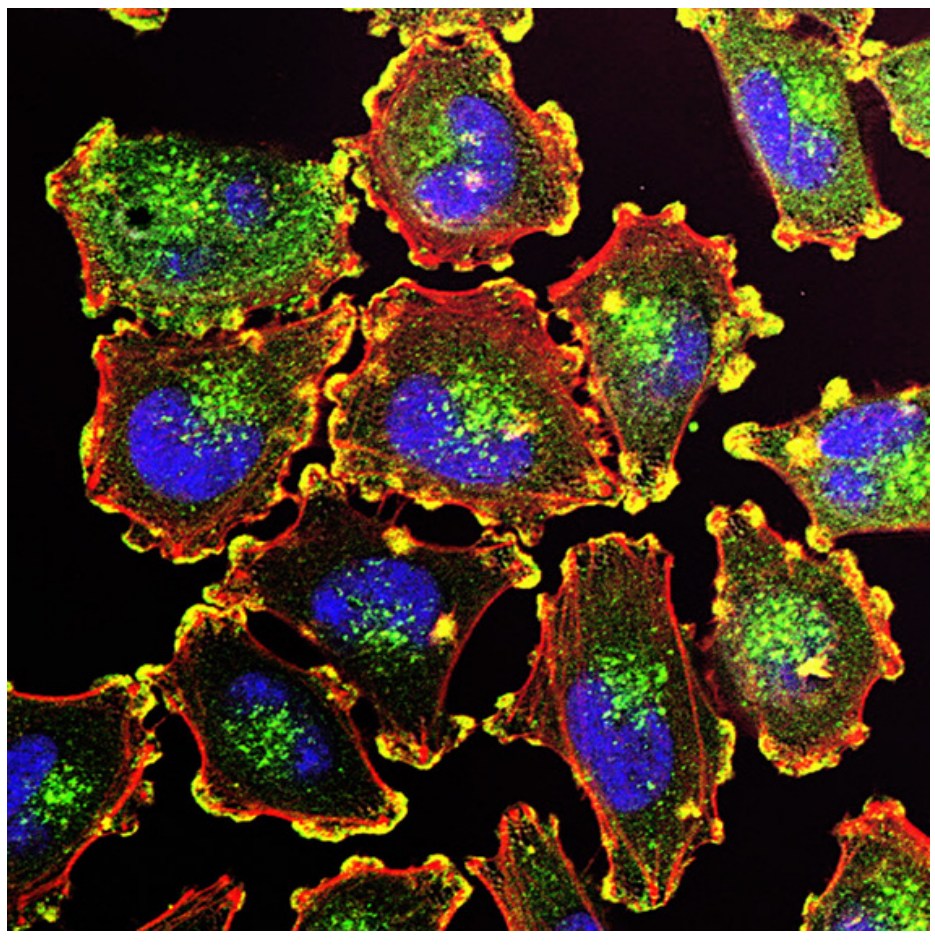
II) Immunotherapy

Immunotherapy includes drugs that are intended to activate or increase immunological activity against the patient's neoplasm.

Immune checkpoint inhibitors (ICIs)

The patient survival in several metastatic solid organ tumors has significantly improved by immunotherapy, but these generally results in immune-related adverse events (IRAEs) including hepatotoxicity in both clinical trials and post-marketing set-up.

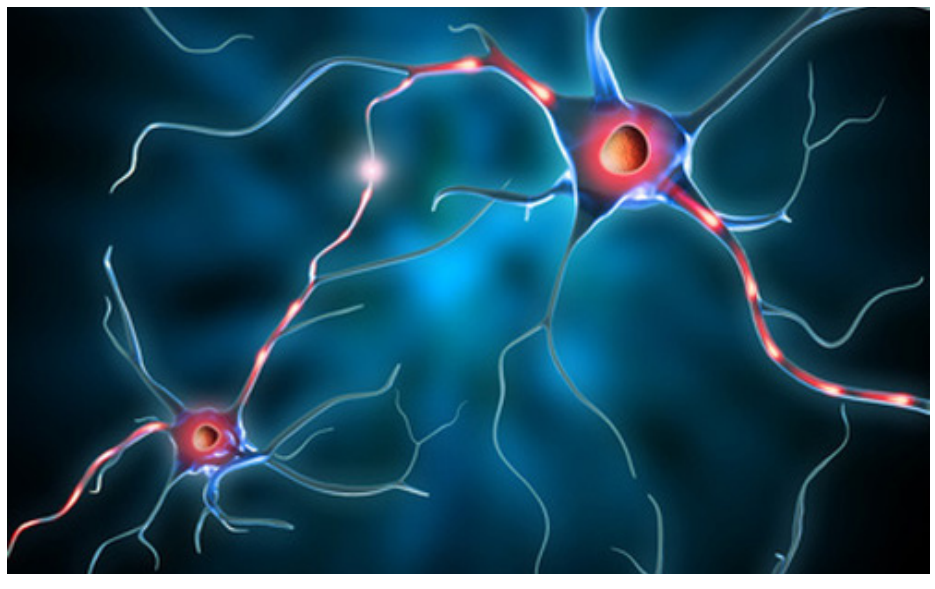
The use of hepatotoxic immunotherapy drugs and/or biological agents with certain other cancer drugs may result in more severe hepatotoxicity than treatment with each single drug.



The hepatic abnormalities with ICIs may range from asymptomatic increases in aminotransferases to acute hepatitis resulting in fulminant hepatic failure. These usually occur 6 to 14 weeks after initiation of treatment, although liver injury can occur after longer treatment duration and even after drug discontinuation.

Protein kinase inhibitors

The protein kinases whose activities are altered in cancer cells are specifically targeted by these anticancer drugs. The clinically evident liver injury with many protein kinase inhibitors is usually self-limited but may be fatal with some drugs and may be hepatocellular or cholestatic.



Features of autoimmunity have been observed in some cases of protein kinase-induced DILI, suggesting that the liver injury may be caused by an immunological autoreactive reaction. Imatinib and nilotinib have been linked to the reactivation of hepatitis B that may be due to the potentiation of hepatitis B virus replication or due to the drug's immunosuppressive effects.

Many of the protein kinase inhibitors have been on the market only for just a few years and there is currently limited understanding as to why protein kinase inhibitors are hepatotoxic. Although there are various mechanisms that may explain the hepatotoxicity with many of these drugs, there is not enough scientific evidence in this area to make solid conclusions.

An overview of some of the newer cancer drugs and their currently known hepatotoxic potential is provided in the figure below:

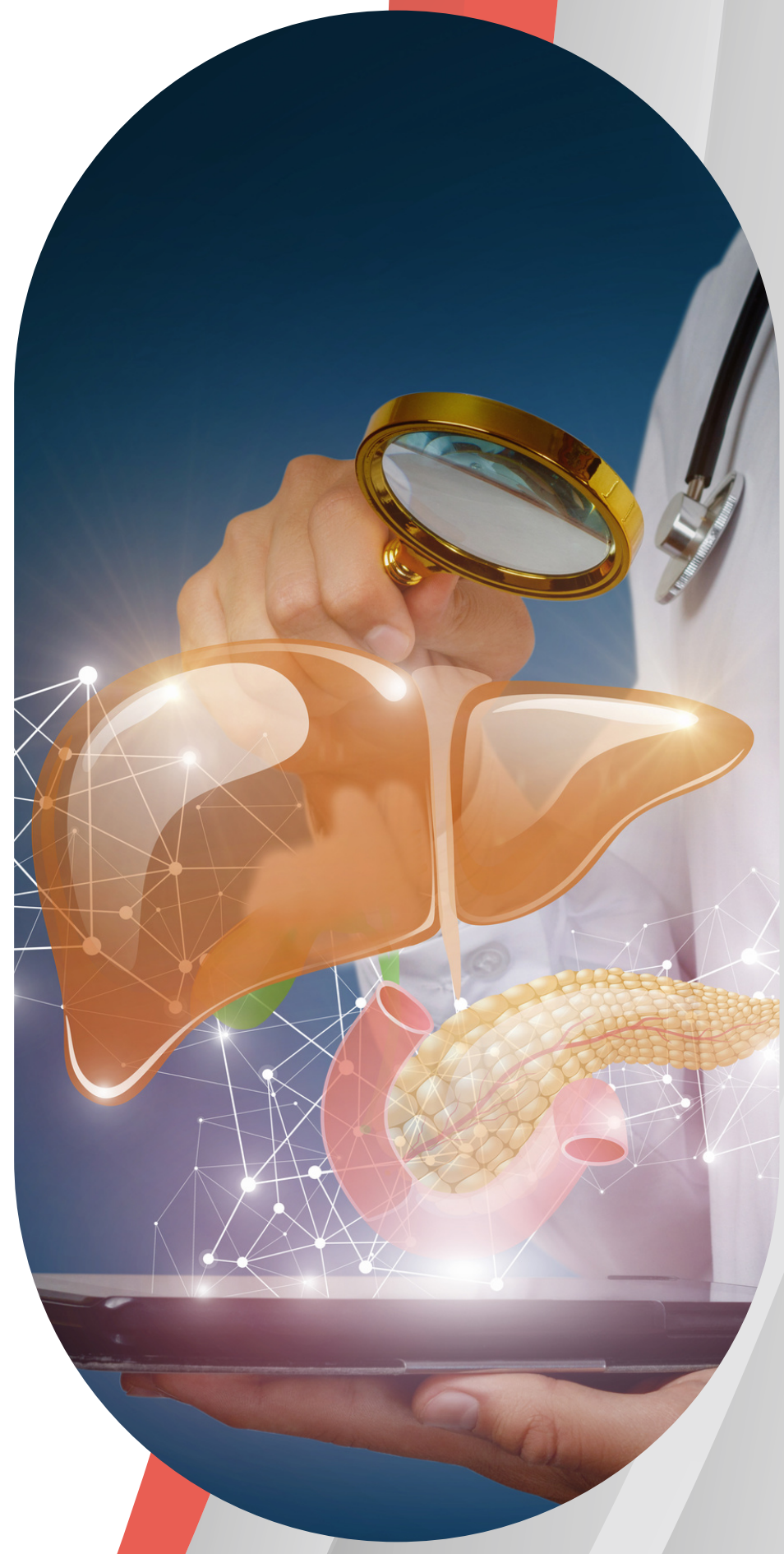
Currently Known Hepatotoxic Potential of Newer Cancer Drugs

Drug class	Mechanism of action	Examples	Currently Observed Liver Injury Potential
Immune checkpoint inhibitors (ICIs)	Blocks cell surface activities of CTLA-4, PD-1 or PD-L1 to stimulate anti-tumor immune responses	• **CTLA-4 inhibitor:** ipilimumab • **PD-1 inhibitors:** pembrolizumab, nivolumab • **PD-L1 inhibitors:** atezolizumab, durvalumab	Immune-mediated liver injury including hepatitis (a) with some distinct histological patterns (b)
Antibody drug conjugates (ADCs)	Cytotoxic drugs covalently linked to monoclonal antibodies directed to antigens differentially overexpressed in tumor cells	• Gemtuzumab ozogamicin • Trastuzumab deruxtecan • Trastuzumab emtansine	Most but not all ADCs are associated with liver toxicity, including fatal liver failure. Pattern of liver injury may differ depending on the toxophore.
Alpha-specific VEGF inhibitor and PD1/PDL-1	(In combination): VEGF inhibitors may potentiate the effect of PD1/PDL-1	• Pembrolizumab plus axitinib • Avelumab plus axitinib	These combination treatments with axitinib increase the rates of higher CTCAE grades of hepatotoxicity.

It can be difficult to characterize the risk of DILI because of low occurrence of event, limited information available, and uncertainties in pathogenesis.

In a real-world scenario, post-marketing risk management is vital to manage the risk of DILI. This is accomplished by periodic reviews and updates to the safety profile of a drug along with risk minimization measures. The product label is the basic information for healthcare professionals to refer for product safety and efficacy and which contains both preclinical and clinical information in a structured format. The product label discusses product risks in the patient population who may potentially be treated with the drug.

Risk stratification is a method for determining and predicting the possibility of a specific outcome among patients who may be exposed to certain anticancer drugs. The product label forms the basis of risk stratification by which the risks of the drug are communicated with the patients who may be treated with the drug. A risk management plan may be effective to manage the risk of DILI if the risk factors are characterized, if there are well defined patterns of liver injury, and/or there are reliable measures on which risk management and monitoring can be based upon.



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At Soterius, our team of experienced physicians and pharmacovigilance professionals perform comprehensive and thoughtful analysis of safety information with novel anti-cancer therapies such as Immune checkpoint inhibitors, Protein kinase inhibitors, PERK inhibitors etc. to monitor any safety concerns including hepatotoxicity.

Please do reach out to connect@soterius.com for more information if you require any support in safety monitoring (SAE Processing, Global Literature Search, Signal Detection, DSURs etc.) for your products and our experts would be happy to connect with you.

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Dr. Sumit Verma is a medical graduate with specialization in anesthesiology and has more than 15 years of experience in the pharmaceutical industry, clinical medicine, clinical research, and pharmacovigilance. He has built teams that have consistently delivered and exceeded customer expectations across pharmacovigilance domains such as case processing, signal management, risk management, aggregate reports, and clinical safety. He has co-authored two books – one on pharmacovigilance and another on pharmacology.

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We support companies from the initial development stage of a drug/vaccine to the approval and ultimate marketing of the therapy, supporting ongoing operations and regulatory commitments globally.