CANCER CHEMOTHERAPY AND HEPATOTOXICITY: AN UPDATE

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Article history
Received 24/06/2014
Available online 08/07/2014

Keywords
Chemotherapy, Tumor, Liver, Toxicity.

ABSTRACT
Cytotoxic chemotherapy prolongs survival of patients with advanced and metastatic tumors. Since the liver has a rich blood supply and plays an active role in the metabolism of medications, it is not surprising that there can be hepatic toxicity related to chemotherapy. In addition, radioembolization may affect the parenchyma of normal and cirrhotic livers. The administration of chemotherapy is a challenge for the tight regulation and balance of these processes. As most drugs tend to be lipophilic, they are readily taken up by the liver. Under chemotherapy, up to 85% of patients develop liver steatosis. Steatohepatitis is the more serious event, especially if accompanied by an increase in bilirubin levels. Modern understanding of the efficacy, safety and tolerability of combination chemotherapy has to increasingly include the individual context of a patient, such as age, gender, nutritional status, underlying diseases, genetic predisposition, as well as the cross-reactivity of the different drugs. This review tries to capture the various effects of chemotherapy on the liver and highlight the pharmacogenomics of such liver insults.


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INTRODUCTION

Normal functioning hepatocytes are a prerequisite for the administration of chemotherapy. In case of abnormalities due to hepatocellular damage or a high demand for hepatocellular biosynthesis, this high-powered engine may yet into trouble. For the correct execution and tight regulation of these processes, the spatial relationship of the hepatocytes with the different cellular structures of the liver is crucial. Changes in the function of the liver immune cells have been reported after cytotoxic chemotherapy. Alongside functional issues, obstruction of the bile duct system prior to chemotherapy presents a problem in cancer patients which has to be solved before chemotherapy is started. Disturbance of the bile flow leads to reduction in the hepatocellular function and to reduced protein synthesis. Nausea and vomiting reduce the uptake of chemotherapy, giving rise to a classification of agents with high or low potential hepatotoxicity (Table 1) [4].

**TOTYC FO TCAPM NOITCNUF REVIL NO YPAREHTOMEHC CIXO**

Most drugs tend to be lipophilic compounds that are taken up readily by the liver but that cannot be excreted easily unchanged in bile or urine. Metabolic pathways are inducible and include a series of steps that alter the parent molecule into a series of steps that alter the parent molecule into a group of intermediate metabolites that are then excreted in the bile. Under chemotherapy, up to 85% of patients develop liver steatosis indicating disturbed lipid metabolism via altered lipoprotein synthesis in the hepatocytes. An increase of the hepatocellular lipid content is responsible for higher vulnerability. The higher vulnerability may, in particular during repeated chemotherapy, induce irreversible hepatocellular damage through recruitment of inflammatory cells. Elevation of serum aminotransferases represents a frequent event during or after cytotoxic chemotherapy. The hepatocellular sensitivity to cytotoxic chemotherapy depends on the particular chemotherapeutic agent, giving rise to a classification of agents with high or low potential hepatotoxicity (Table 1) [4].

**Table 1. Hepatotoxicity of cytotoxic chemotherapeutics.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Hepatotoxicity</th>
<th>Hepatotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>+++</td>
<td>Streptozotocin</td>
</tr>
<tr>
<td>Asparaginase</td>
<td>++</td>
<td>Busulfan</td>
</tr>
<tr>
<td>Carmustine</td>
<td>++</td>
<td>Cisplatin</td>
</tr>
<tr>
<td>Mercaptopurine</td>
<td>++</td>
<td>5-FU</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>+</td>
<td>Irinotecan</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>+</td>
<td>Imatinib</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>+</td>
<td>Oxaliplatin</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>+</td>
<td>Vincristine</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>+</td>
<td>Bevacizumab</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>+</td>
<td>Cetuximab</td>
</tr>
<tr>
<td>Etoposide</td>
<td>+</td>
<td>Epirubicin</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>+</td>
<td>Hydroxyurea</td>
</tr>
<tr>
<td>Mitomycin C</td>
<td>+</td>
<td>Rituximab</td>
</tr>
</tbody>
</table>

+++ Very often. ++ Often. + Rare. ± Very rare. 0 no hepatotoxicity

The clinical patterns of liver injury are defined as hepatocellular, with a predominant initial elevation of the alanine aminotransferase level (ALT), cholestatic, in which the serum alkaline phosphatase concentrations are increased or mixed, if both enzymes are elevated. An ALT level of more than three times the upper limit of normal values and a total bilirubin concentration of more than twice the upper limit are used to define clinically significant abnormalities. Elevation in serum enzyme levels is taken as an indicator of liver injury, whereas increases in bilirubin levels, albumin concentration and the prothrombin time are measures of overall liver function [5]. With acute leukemia Chemotherapy-induced hepatotoxicity is a common cause of abnormal liver function. This mainly occurs in an idiosyncratic manner and is generally reversible and nonfatal. This toxicity is manifested in a variety of patterns. In addition to those mentioned above, bile duct obstructions, ductal injury, fibrosis, cirrhosis, veno-occlusion, peliosis hepatis, and nodular regenerative hyperplasia. The two latter lesions appear as pseudotumors that may indicate disease progression, especially if they are multiple [6]. Hepatotoxicity usually begins with vague clinical symptoms such as fatigue, anorexia, nausea, dark urine, right upper quadrant discomfort and jaundice. Suspected drug exposure must precede the symptoms and liver injury may improve when administration is stopped. However, the latent period is highly variable and enzyme levels may take weeks to increase. Before attributing these symptoms to a chemotherapy drug, other causes of liver injury must be ruled out [5]. [Abnormal liver function may be due to multiple causes in patients with acute leukemia. Leukemic infiltration usually causes mild to moderate hepatomegaly with limited impact on serum transaminase levels. Transfusions increase the likelihood of viral hepatitis. Other circumstances such as sepsis, hypotension or malnutrition may contribute to liver damage. Acute leukemia patients are treated with combination chemotherapy, making it difficult to identify the precise agent involved in the hepatic injury.

Moreover, diagnosis becomes more challenging by the large number of non-chemotherapeutic drugs commonly used in those patients, some of them holding the potential of being hepatotoxic, e.g. allopurinol, ondansetron and different antifungal agents. Pre-existing liver disease can alter the metabolism and excretion of chemotherapy causing increased and persistent drug levels and hence systemic toxicity. On the other hand, chemotherapy may worsen liver disease, such as occurs with hepatitis. Severe liver dysfunction

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and fatal fulminant hepatitis through virus reactivation have been described in patients with viral hepatitis. Prophylactic therapy with nucleoside analogues, typically lamivudine, has been recommended for HBsAg positive patients. This strategy has been reported to allow optimal administration of chemotherapy [7].

The mechanism of chemotherapy-induced hepatic injury is thought to be secondary to production of reactive oxygen species (ROS), intended to induce tumor cell apoptosis. Previously steatotic livers were thought to be most susceptible to chemotherapy-induced injury due to impaired regenerative capability and abnormal innate immunity [8].

Decrease in excretion of toxic components associate with Depletion of cytochrome P450 involved in the metabolism of drugs that enters the body and cause their accumulation in organs and tissues, disrupt neutralization of endogenous metabolic products or may result in the formation of secondary, sometimes more toxic than the original product substances. In addition, as the removal of harmful substances in the liver stes problematic, anticancer drugs can cause cumulative toxic effect on its functional state. Portal hypertension due to severe fibrosis may be the cause of prolonged treatment with cytotoxic drugs. esod hgiHchemotherapy most frequently shows venoocclusive liver disease, Which is special form of liver disease in patients with cancer pathology. The disease is characterized ybyhyperbilirubinemia, rapid growth and tenderness of liver, fluid retention with the development of ascites. One of the long-term effects of exposure is liver fibrosis is Concurrent use of doxorubicin and vincristine potentiate radiation liver injury. Due to the widespread use of cytotoxic and hormonal agents on malignant disease that has significant immunosuppressive effect; patients in this category are extremely susceptible to infectious diseases. So, hepatitis in these patients may also be due to a wide range of infectious agents: nonspecific lesions in the generalized infections, liver abscesses, fungal diseases and viral hepatitis, particularly cytomegalovirus, herpes simplex, herpes zoster dna adenovirus [9]

CONFOUNDER FACTORS
Toxic liver injury can reproduce virtually any known pattern of injury, including necrosis, steatosis, fibrosis, cholestasis, and vascular injury [10]. Liver injury during cancer chemotherapy may not always reflect hepatotoxic anticancer tsum snaicnilc eht os consider reactions to antibiotics, analgesics, antieptics, or other medications. Preexisting medical problems, tumor, immunosuppression, hepatitis viruses and other infections, and nutritional deficiencies or total parenteral nutrition all may affect a host’s susceptibility to liver injury. Attributing liver injury to a toxic reaction is therefore difficult [11, 12]. The liver serves many metabolic functions, yet quantitative markers for liver function are not available in everyday practice. Estimation of liver injury is therefore indirect, and recognizing the severity of hepatic injury can also be problematic. Besides these parameters, abdominal ultrasound or computerized tomography may be needed to identify biliary, vascular, and tumor-related conditions. Notably, liver biopsy is seldom necessary to characterize or stage acute hepatotoxicity [13].

Although many eht fo pharmaceuticals can cause liver injury, most hepatotoxic drug reactions are idiosyncratic, due to immunologic mechanisms or variations in host metabolic response [14]. These reactions are not typically dose-dependent. Less common are dose-dependent, predictable toxic effects of a medication or its metabolites. In general, preexisting liver disease has little effect on elimination and toxicity of most drugs unless Child’s Class C cirrhosis is present [15, 16]. The presence of ascites, however, may make a substantial difference, especially in the case of methotrexate (MTX). In cancer chemotherapy, however, dosing decisions are often made based on limiting toxicity. Therefore, intrinsic hepatotoxicity is of greater concern, and altered hepatic clearance may cause increased non-hepatic toxicity. Nonetheless, systematic data on the hepatotoxic effects of chemotherapy is scant, and the mechanisms of injury are established for few agents. For example, recognizing the importance of macromolecule alkylation in the injury produced by many known hepatotoxins, one would predict much greater toxicity from alkylating agents than is observed in practice [8].

SPECIFIC AGENTS
Mercaptopurine and 6-Thioguanine
6-Mercaptopurine (6-MP) in oral daily regimen associated with weekly metaxartohite is the backbone of maintenance chemotherapy acute lymphoblastic leukemia (ALL). Hepatotoxicity produced by this drug includes both cholestatic and hepatocellular disease. Characteristic diagnostic profiles include prominently elevated serum bilirubin, typically between 3 and 7 mg/dL, accompanied by mild to moderate elevations in aminotransferases and alkaline phosphatase [17]. Liver function tests are transiently abnormal in the majority of children during maintenance ypabrentof ALL.

In the absence of other evidence of severe liver toxicity or viral hepatitis, it is generally not necessary to withhold or reduce the dose of continuation chemotherapy [18].When liver biopsies are performed in this population, inflammatory and fatty changes are common and not related with ALT levels. Early portal fibrosis is found only in patients with prolonged therapy. The risk of portal fibrosis is low after 2-3 years of continuing chemotherapy and most patients go back to normal ALT values with drug cessation. The mechanism underlying 6-MP-induced hepatotoxicity is related to its methylated metabolites and correlates with ALT levels. Indeed, ALT levels have been proposed as a surrogate marker for treatment compliance [19]. A study by Schmiegelow et al. has shown that ALL pediatric patients with mean ALT levels above the upper normal limit (40 IU/l) who were kept on therapy had a significantly lower risk of hematological relapse compared to other children [20]. These data support the concept of treating to toxicity for maintenance therapy. 6-Thioguanine as maintenance treatment in childhood ALL has also been shown to cause hepatic veno-occlusive disease (VOD), usually mild and reversible on withdrawing 6-TG or replacing it with 6-MP [21].

Methotrexate (MTX)
MTX inhibits dihydrofolate reductase resulting in depletion of critical reduced folates. The net result is effective inhibition of DNA and RNA synthesis and potent cytotoxicity to rapidly dividing cells. MTX causes hepatotoxicity, fibrosis and cirrhosis, but
usually after prolonged use and/or when it is used in the treatment of autoimmune diseases. In a high percentage of patients with ALL, MTX causes isolated elevations of ALT during maintenance chemotherapy, usually transient and asymptomatic. This ALT elevation is not predictive of subsequent hepatic disease and do not require treatment modification [22]. As in the maintenance treatment, when MTX is used in high IV doses (HD-IV MTX), the characteristic hepatotoxic pattern is transient, ALT levels are related to the dose of MTX and increase with the number of cycles received. A difference with the maintenance treatment is that in cases of altered hepatic function it is necessary to modify or suspend the administration of HD-IV MTX (Table 2). In any case, despite the usual benign character of MTX-induced hepatotoxicity, there are reports of hepatoma in association with hepatic fibrosis occurring in children following ALL treatment [23].

Cytarabine

Cytarabine (ara-C) results in a cumulative dose-dependent hepatotoxicity. Several case reports have demonstrated direct histologic evidence of a hepatotoxic role for ara-C, expressed as increased ALT levels or as intrahepatic cholestasis. Although the actual incidence of this toxicity remains to be elucidated, mild elevations of liver function in a cholestatic pattern represent the reversible, rarely fatal clinical picture [24]. Ara-C is reported to be partially detoxified in the liver. Therefore, it is recommended that its dose be reduced in patients with liver impairment.

L-Asparaginase

In addition to hypersensitivity reactions, the most common toxic effects of L-asparaginase are related to the depletion of proteins synthesized in the liver such as clotting factors, insulin, albumin, haptoglobin and transferrin. Liver function abnormalities (including hyperbilirubinemia and elevated transaminase levels) and hyperlipidemia (hypertriglyceridemia and hypercholesterolemia) have been frequently reported in patients receiving the drug [25]. As a result of these metabolic abnormalities, up to 7% of children with aicukel euca develop pancreatitis [26]. Another common metabolic complication of this drug is hyperglycemia, which occurs in up to 10% of children with acute aicukel during their induction therapy and which is associated with the synergistic effect of L-asparaginase and glucocorticoids [27]. It should be noted that the use of pegylated asparaginase does not prevent these complications [28].

<table>
<thead>
<tr>
<th>DRUG</th>
<th>HEPATOTOXICITY PROFILE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>1-2% of patients with increased levels of liver enzymes and/or bilirubin in serum.</td>
</tr>
<tr>
<td>Carmustine</td>
<td>90% of patients after one week of therapy develop abnormal liver function (increased transaminases, alkaline phosphatase), hyperbilirubinemia</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>10% of patients demonstrate abnormal liver function with changing parameters of liver function tests (increase in transaminases, alkaline phosphatase and bilirubin).</td>
</tr>
<tr>
<td>Floxuridine</td>
<td>Abnormal liver function appears in 50% of patients using intra-arterial infusion.</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>2% of patients with liver dysfunction, increased gamma glutamyl transferase, bilirubin.</td>
</tr>
<tr>
<td>Daclomycin</td>
<td>15% of patients: ascites, hepatomegaly, hepatitis, liver function tests change.</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>10-29% of patients: transient increase in transaminases in 15-20% - increased alkaline phosphatase and bilirubin.</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>10% of patients diagnosed with liver dysfunction with an increase in liver transaminases and/or bilirubin.</td>
</tr>
<tr>
<td>Interleukin-2</td>
<td>Higher bilirubin in 40% patients.</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>17% patients: transient increased transaminases; High doses cause toxic hepatitis, fibrosis and cirrhosis.</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>3% patients may develop jaundice; 10% abnormal liver function (increased levels of bilirubin and transaminases).</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Increased levels of alkaline phosphatase and bilirubin; Hepatic necrosis and hepatic encephalopathy are common.</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>2-10% patients develop liver dysfunction with increased levels of liver enzymes and/or hyperbilirubinemia.</td>
</tr>
<tr>
<td>Melphalan</td>
<td>Transient liver dysfunction using high doses in 10% patients.</td>
</tr>
</tbody>
</table>

According to WHO recommendations, five degrees of intensity of esrveda effects of anticancer drugs eb nac distinguished (Table 3).
Table 3 : Evaluation of toxicity (WHO)

<table>
<thead>
<tr>
<th>Index</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin</td>
<td>&lt;18.81 mmol / l</td>
<td>N</td>
<td>1.26-2.5xN (upper limit of normal)</td>
<td>2.6-5xN (upper limit of normal)</td>
<td>5.1-10xN (upper limit of normal) ≥ 10xN</td>
</tr>
<tr>
<td>ALT</td>
<td>&lt;40 U / l</td>
<td>N</td>
<td>1.26-2.5xN (upper limit of normal)</td>
<td>2.6-5xN (upper limit of normal)</td>
<td>5.1-10xN (upper limit of normal) ≥ 10xN</td>
</tr>
<tr>
<td>AST</td>
<td>&lt;40 U / l</td>
<td>N</td>
<td>1.26-2.5xN (upper limit of normal)</td>
<td>2.6-5xN (upper limit of normal)</td>
<td>5.1-10xN(Upper limit of normal) ≥ 10xN</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>35-129 U / l</td>
<td>N</td>
<td>1.26-2.5xN (upper limit of normal)</td>
<td>2.6-5xN (upper limit of normal)</td>
<td>5.1-10xN (upper limit of normal) ≥ 10xN</td>
</tr>
<tr>
<td>Gamma glutamyl transferase</td>
<td>5-61 IU / l</td>
<td>N</td>
<td>1.26-2.5xN (upper limit of normal)</td>
<td>2.6-5xN (upper limit of normal)</td>
<td>5.1-10xN (upper limit of normal) ≥ 10xN</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>&lt;5.2 mmol / l</td>
<td>N</td>
<td>1.26-2.5xN (upper limit of normal)</td>
<td>2.6-5xN (upper limit of normal)</td>
<td>5.1-10xN (upper limit of normal) ≥ 10xN</td>
</tr>
<tr>
<td>Clinical</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Precoma</td>
<td>Hepatic coma</td>
</tr>
</tbody>
</table>

N - Upper limit of normal

Antitumor antibiotics

The antitumor antibiotics include doxorubicin, daunorubicin, mitoxantrone, bleomycin, mitomycin, mithramycin (plicamycin), and dactinomycin. Doxorubicin, an anthracycline antibiotic, acts through DNA intercalation, alteration of membrane function, and free radical formation. It is extensively metabolized in the liver and liver antioxidant capacity, including that provided by glutathione production may protect against free radical injury. Benjamin described eight patients with impaired liver function who developed severe pancytopenia and mucositis while receiving doxorubicin. This experience led to recommendations for dose reductions for altered hepatic function, but hepatotoxicity from doxorubicin is rare. In one series, six patients with acute lymphoblastic leukemia were treated with induction therapy using vincristine, prednisone, and doxorubicin. Shortly after administration, increases in AST, ALT, and bilirubin were seen, with focal infiltration by inflammatory cells and steatosis on liver biopsies. This was considered an idiosyncratic reaction. Mitoxantrone, an anthraquionone antibiotic, may have a lower incidence of serious toxicities than other anthracycline anticancer drugs. When used in leukemic patients, the drug has produced transient elevations in AST and ALT levels [29]. Bleomycin is composed of several polyptides and exerts its effect by single-strand scission of DNA, which may lead to breakage of double-stranded DNA. Because it does not cause myelosuppression, it is often used in combination with other chemotherapeutic agents for lymphomas, testicular carcinomas, and various squamous carcinomas. Bleomycin is excreted in the urine and inactivated by an aminopeptidase present in many tissues, including liver. The lungs and skin lack this aminopeptidase and are thus susceptible to injury from bleomycin. Most human studies have found a very low incidence of liver dysfunction; a review of more than 1,000 patients treated with bleomycin concluded that hepatic toxicity was not consistently reported, nor could it be specifically ascribed to bleomycin [30]. Mitomycin is an antitumor antibiotic but acts as an alkylating agent, primarily by inhibiting DNA synthesis. The metabolism of the drug is unclear, but it is found in high concentrations in the bile. Since urinary excretion cannot account for its rapid clearance, it has been suggested that mitomycin is cleared from the serum by metabolism [31]. Although mitomycin has a broad spectrum of antitumor activity, it has a low level of efficacy. The article that reported abnormalities in liver function tests did not discuss the patients’ clinical states [32]. Plicamycin (mithramycin) is the most hepatotoxic chemotherapeutic agent commercially available [33, 34]. With the discovery of less toxic and more effective drugs, it is now rarely used except for the treatment of tumor hypercalcemia refractory to other therapy. The drug binds to DNA and is a potent inhibitor of RNA transcription from DNA. Subsequent reduction in messenger RNA synthesis brings a secondary inhibition of the production of enzymes. Plicamycin could thus block the production of many intracellular enzyme systems necessary for normal hepatic function. Elevations of aminotransferases (often to enormous levels) and LDH occur in virtually 100% of patients treated with plicamycin. Milder elevations in alkaline phosphatase occur, but serum bilirubin is usually normal. These changes begin on the day of drug administration, peak on the second day, and return to normal by 4 to 21 days after treatment [35].

Dactinomycin has produced hepatotoxicity, seen as transient AST elevations, in children who have received radiotherapy with fields involving the liver. Since dactinomycin is known to produce a recall reaction in tissues previously irradiated, it is possible that its administration reactivates prior radiation damage to the liver. The administration of chemotheraphy following hepatic radiation has been marked by greater than anticipated leukopenia and thrombocytopenia, suggesting that radiation-induced hepatic toxicity prolongs excretion and thus toxicity of the drug [36]. In another trial of Wilms’ patients, hepatotoxicity occurred in 13% of subjects given dactinomycin on five consecutive days and 0% of those treated with a double dose on a single day [37]. The United Kingdom Children’s Cancer Study Group’s Wilms’ Tumor Trial also reported hepatotoxicity associated with pulsed dactinomycin [38].
Spindle inhibitors

Vincristine is excreted primarily by the liver but has seldom been implicated as a hepatotoxin. It scudorp hepatotoxicity when used in combination with radiation. Transient aminotransferase elevations, confirmed on rechallenge, have also been reported in a single case [39]. Alkaline phosphatase elevations predict delayed clearance of vincristine and may lead to increased neurotoxicity [40]. Paclitaxel (Taxol) and docetaxel (Taxotere) are members of the newest class of spindle inhibitors. They work by a different mechanism, binding to microtubules rather than tubulin dimers. Both are extensively excreted by the liver, and caution is warranted in patients with liver impairment. With paclitaxel, elevation from baseline hepatic functions (bilirubin, 8%; alkaline phosphatase, 23%; transaminase, 33%) was seen in 4% to 17% of patients treated with doses of less than 190 mg/m2 and in 16% to 37% of patients treated at higher doses [41]. A recent report, however, identified three patients who experienced severe hepatocellular injury at standard doses [42]. At high doses, etoposide induces hyperbilirubinemia, elevated aminotransferases, and elevated alkaline phosphatase activity approximately three weeks after administration [43, 44]. These cleared over 12 weeks without sequelae. Elevated serum bilirubin levels have been correlated with subsequent leukopenia [45]. There are two topoisomerase I inhibitors currently available, irinotecan and topotecan. Irinotecan is metabolized in the intestine, plasma, and liver. Its active metabolite, SN-38, is inactivated by glucuronidation in the liver. It has been used in colorectal, ovarian, and lung cancers. Elevations of serum transaminases and bilirubin occur in up to 25% of patients [46]. Topotecan, in contrast, is not extensively metabolized and a significant portion is excreted in the urine. It is used in ovarian cancer and myelodysplastic syndromes. Low-grade and reversible elevations in alkaline phosphatase and transaminases have been seen in 5%-8% of patients [47]. Topotecan may be safely used with bilirubin levels up to 10 mg/dl, but no specific recommendations regarding irinotecan can be given.

Platinums

Cisplatin is a rare cause of hepatic toxicity (steatosis and cholestasis) at standard doses [48], but minor AST elevations are not uncommon [49]. At high doses, it has been reported to produce abnormal liver tests, especially AST and ALT [50]. Cisplatin-induced acute hepatic injury is dose-related. Carboplatin is a cisplatin derivative developed to meet the need for a platinum compound with a better therapeutic index. A case of carboplatin-induced liver failure has been reported [51]. A case of autopsy-documented hepatic veno-occlusive disease has been reported in a patient who received high-dose carboplatin and etoposide [52]. Although multiple other medications were given, the potential role of carboplatin in the production of liver disease deserves mention.

COMBINATION CHEMOTHERAPY

The development of combination chemotherapy produced new evidence of hepatotoxicity, and more instances can be anticipated in the future. Combination chemotherapy uses several chemotherapeutic agents, each with a different mechanism of action and toxicity profile. Along with the potential for greater tumor kill, however, the possibility for enhanced toxicity occurs. The addition of 6-MP to doxorubicin (Adriamycin) to treat refractory leukemic patients produced an example of this phenomenon [53]. Hyperbilirubinemia and elevated levels of AST and alkaline phosphatase increased with each course and returned to normal between treatments. Liver tissue at autopsy showed intrahepatic cholestasis, hepatocellular necrosis, leukemic infiltration, or fatty change. The investigators felt that the intracellular accumulation of doxorubicin may have potentiated the hepatotoxic effects of 6-MP. Hepatic nodular regenerative hyperplasias (NRH) was observed in patients with chronic granulocytic leukemia treated with the combination of busulfan and 6-thioguanine [54]. NRH is characterized by diffuse nodules of regenerative hepatocytes, without the fibrous septa of cirrhosis, and there is no progression to cirrhosis. The syndrome may be clinically silent or progress, as in the cases reported, to portal hypertension. As in veno-occlusive disease, the initiating injury is believed to be vascular, in this case to the portal vein branches [55]. When high doses of both bis-chloroethylnitrosourea (BCNU) and etoposide were used to treat high-grade glioma [56], two of four patients developed ascites, hyperbilirubinemia, and thrombocytopenia and died; a third had transient ascites. Many of the agents used in the treatment of acute lymphoblastic leukemia are potential hepatotoxins, but there have been few instances of documented hepatotoxicity. This may be related to the means of detection used; although light microscopic changes were minimal, electron microscopic examination of liver biopsy specimens from children given MTX and 6-MP showed significant abnormalities in all patients [57]. In another study, liver biopsy specimens from children receiving maintenance therapy with 6-MP and MTX revealed mild inflammatory and fatty changes in many, and early portal fibrosis in 3 of 16 biopsies after more than two years of therapy [58]. Interpretation of reported cases has been complicated by the fact that children who present at an older age and require more transfusions are more likely to develop increased ALT values in a pattern consistent with non-A, non-B hepatitis [59]. Adjuvant chemotherapy for breast cancer with cyclophosphamide, MTX, and 5-FU has produced both abnormal liver tests and focal defects on radionuclide scans [60]. Liver biopsy specimens showed severe local inflammation.

A larger study using cyclophosphamide and 5-FU, with doxorubicin replacing MTX as adjuvant therapy, found that 77 patients developed liver function abnormalities [61]. These abnormalities appeared within the first three months of therapy and normalized in 90 patients within a year of cessation of treatment. A cholestatic hepatitis picture was seen in a patient receiving flotafur, doxorubicin, and cyclophosphamide [62]. In this setting, liver biopsy may be necessary to exclude tumor metastases and confirm the impression of drug-induced changes. Hepatic lobatum, previously seen almost exclusively with healed or tertiary syphilis, has also been described in association with combination chemotherapy for breast cancer [63]. While the addition of 5-iodo-2' deoxyuridine to 5-FU did not increase hepatotoxicity, the addition of leucovorin produced greater toxicity than FUDR alone [64]. In the adjuvant setting, intrahepatic 5-FU and mitomycin combined with hepatic irradiation produced elevations in liver enzymes and chronic liver damage with one death [65]. The combination of N-phosphonomethyl-aspartate and 5-FU caused transient hepatic abnormalities in 15 of 17 patients, with ascites, hyperbilirubinemia, and hypoaalbuminemia [66]. The combination of 5-FU and levamisole, used as adjuvant therapy for resected stage III colon cancer, also carries the potential for hepatotoxicity. In a series of
1,025 patients treated in a randomized trial of observation alone, levamisole, or the combination of 5-FU and levamisole, 39% of patients receiving both drugs showed laboratory abnormalities consistent with hepatic toxicity [67]. Elevations of alkaline phosphatase were most common, followed by elevations of transaminases or serum bilirubin. These changes were asymptomatic and resolved when therapy was stopped. They were occasionally associated with rises in carcinoembryonic antigen (CEA) or with fatty liver on CT scan or liver biopsy. The pattern of abnormal liver function tests and abnormal CT scan may lead the unwary to inappropriately conclude that the patient’s disease is progressing. Reversible hepatic steatosis was seen in approximately 30 patients with metastatic colorectal cancer treated with the combination of α-interferon and 5-FU [68]. The changes all reversed with the cessation of therapy, but recognition of this condition is essential to avoid an erroneous label of progressive disease. Apparently otherwise tolerable doses of irradiation can induce severe injury when combined with chemotherapeutic agents that in themselves are also unlikely to produce toxicity. Vincristine produced severe hepatic toxicity when given in conjunction with abdominal radiation therapy for lymphoma. Another case of fatal acute radiation hepatitis occurred in a patient with non-Hodgkin’s lymphoma, who had received abdominal irradiation (2,250 rads to the liver) and vincristine [69]. A similar phenomenon has been described with radiation and doxorubicin [70] or radiation alone [71].

Many drugs without antineoplastic effects may cause hepatoxicity. Intensive chemotherapy has been implicated in the development of fatal hepatic necrosis following halothane anesthesia. Allopurinol, commonly given with chemotherapy to prevent uric acid nephropathy and secondary gout, has also been linked to fulminant hepatic failure, presumably due to a hypersensitivity reaction. There is also a report of allopurinol hepatotoxicity possibly potentiated by an interaction with tamoxifen. Several cases of fatal, massive hepatic necrosis and others of liver damage have been attributed to ketoconazole. These are also thought to be idiosyncratic reactions. Fluconazole may cause hepatitis but has been reported to cause abnormal liver enzymes without significant liver biopsy changes. The antiemetic ondansetron has been implicated in hepato cellular injury and jaundice. The current popularity of alternative medicines has led to the recognition of herbal hepati tis. Specific inquiry about such nonstandard agents is particularly important when hepatotoxicity occurs in the outpatient setting. Hepatitis has also been attributed to G-CSF, and CSF-secreting tumors may cause paraneoplastic hepatitis. Finally, a syndrome of hyperammonemia has been reported in patients who have received high-dose combination chemotherapy for hematologic neoplasms. This syndrome is characterized by progressive mental status changes, respiratory alkalosis, and markedly elevated plasma ammonium levels. Mildly elevated liver tests have been seen in some patients, but the etiology of this is not clear] 32.

CONCLUSIONS
Chemotherapeutic agents, alone or in combination, may cause hypersensitivity reactions or direct hepatic toxicity, and altered liver function may alter drug metabolism and cause an increased risk of nonhepatic toxicity [72]. Guidelines on dose modification in hepatic disease are largely empiric. The facts that enil mottob clinical judgment and a high index of suspicion remain critical tools in preventing and treating hepatic manifestations of cancer chemotherapy.

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