Hepatotoxicity of Chemotherapy

PAUL D. KING,a MICHAEL C. PERRYb

aGastroenterology and Hepatology, bHematology and Medical Oncology, Department of Internal Medicine, University of Missouri-Columbia, Columbia, Missouri, USA

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ABSTRACT

After assessment of tumor histology, the next important factor to consider in the selection of a chemotherapy regime is organ function. Patients who are to receive chemotherapy require careful assessment of liver function prior to treatment to determine which drugs may not be appropriate, and which drug doses should be modified. Following therapy abnormalities of liver function tests may be due to the therapy rather than to progressive disease, and this distinction is of critical importance. Furthermore, not all abnormalities in liver function are due to the tumor or its treatment, and other processes, such as hepatitis, must be kept in mind. This article reviews the hepatic toxicity of chemotherapeutic agents, and suggests dose modifications based upon liver function abnormalities. Emphasis is placed on agents known to be hepatotoxic, and those agents with hepatic metabolism. The Oncologist 2001;6:162-176

INTRODUCTION

Toxic liver injury can reproduce virtually any known pattern of injury, including necrosis, steatosis, fibrosis, cholestasis, and vascular injury [1]. Liver injury during cancer chemotherapy may not always reflect hepatotoxic anticancer drugs; the clinician must also consider reactions to antibiotics, analgesics, antiemetics, 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 [2, 3].

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. Table 1 outlines the hepatic Common Toxicity Criteria of the National Cancer Institute, version 2.0. 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 [4].

Although many pharmaceuticals can cause liver injury, most hepatotoxic drug reactions are idiosyncratic, due to immunologic mechanisms or variations in host metabolic response [5]. 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 [6, 7]. 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 nonhepatic toxicity. Nonetheless, systematic data on the hepatotoxic effects of chemotherapy are 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. This review discusses the effects of chemotherapeutic agents on the liver and updates our previous review [8]. Other reviews have been published [9-15]. The reader is referred to other texts for more detailed descriptions of the pharmacology of chemotherapeutic agents [16, 17].

Correspondence: Michael C. Perry, M.D., Division of Hematology/Oncology, University of Missouri Ellis Fischel Cancer Center, 115 Business Loop 70 West, Columbia, Missouri 65203, USA. Telephone: 573-882-4979; Fax: 573-884-6050; e-mail: perrym@health.missouri.edu Received September 15, 2000; accepted for publication February 5, 2001. ©AlphaMed Press 1083-7159/2001/$5.00/0

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ALKYLATING AGENTS

The alkylating agents include the nitrogen mustards, ethylenemines, alkylsulfonates, nitrosoureas, and triazines. Five nitrogen mustards are currently used in therapy: mechlorethamine, cyclophosphamide, ifosfamide, melphalan, and chlorambucil.

Mechlorethamine, given intravenously, rapidly undergoes chemical transformation and combines with either body water or reactive compounds. Hepatic metabolism is not considered important, and nitrogen mustard does not cause hepatic abnormalities [15], presumably because of its rapid degradation.

In an attempt to achieve greater selectivity for neoplastic tissues, the chemical structure of mechlorethamine was modified, resulting in cyclophosphamide. The liver cytochrome P450 system converts cyclophosphamide to 4-hydroxycyclophosphamide, which is in equilibrium with its acyclic tautomeric form, aldophosphamide. In cells susceptible to cytolysis, nonenzymatic cleavage of aldophosphamide yields phosphoramide mustard and acrolein. These two compounds are highly cytotoxic and may represent active forms of the drug. Although it has hepatic metabolism, cyclophosphamide can be given in the face of elevated liver enzymes and/or bilirubin.

In spite of its requirement for hepatic metabolism for activity, cyclophosphamide is an uncommon hepatic toxin, and only a few reports of elevated hepatic enzymes are attributed to the drug [18-23]. This effect is likely due to an idiosyncratic reaction rather than direct toxicity.

When used to treat vasculitis, cyclophosphamide has been associated with liver damage when its administration was preceded by azathioprine [23]. Biopsy in three of the four patients in this report showed liver cell necrosis. In two patients, cyclophosphamide had previously been given without antecedent azathioprine, and hepatic injury had not been seen, suggesting an apparent interaction of the two drugs to cause liver cell necrosis.

Ifosfamide is a related oxazaphosphorine and requires hepatic P450 mixed-function oxidases for activation to active intermediates. It also undergoes hepatic activation to an aldehyde form that decomposes in plasma and peripheral tissues to yield acrolein and its alkylating metabolite [16]. Dose modifications are probably not needed for altered liver function.

Melphalan is rapidly hydrolyzed in plasma, and approximately 15% is excreted unchanged in the urine. At usual doses, it is not associated with hepatotoxicity, but it does produce transient abnormalities in liver function tests at the

**Table 1. CTC hepatic toxicity criteria**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Alkaline phosphatase</th>
<th>Bilirubin</th>
<th>Bilirubin associated with graft-versus-host-disease (GVHD) for BMT studies, if specified in the protocol.</th>
<th>GGT (γ-Glutamyl transpeptidase)</th>
<th>Hepatic enlargement</th>
<th>Hypoalbuminemia</th>
<th>Liver dysfunction/failure (clinical)</th>
<th>Portal vein flow</th>
<th>SGOT (AST) (serum glutamic oxaloacetic transaminase)</th>
<th>SGPT (ALT) (serum glutamic pyruvic transaminase)</th>
<th>Hepatic—other</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>WNL</td>
<td>WNL</td>
<td>Normal ≥2-&lt;3 mg/100 ml</td>
<td>WNL</td>
<td>Absent</td>
<td>WNL</td>
<td>Normal</td>
<td>Normal</td>
<td>WNL &gt;ULN-2.5 × ULN</td>
<td>WNL &gt;ULN-2.5 × ULN</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>&gt;ULN-2.5 × ULN</td>
<td>1.5 × ULN</td>
<td>≥3-&lt;6 mg/100 ml</td>
<td>&gt;ULN-2.5 × ULN</td>
<td>—</td>
<td>&lt;LLN-3.0 g/dl</td>
<td>—</td>
<td>—</td>
<td>&gt;2.5-5.0 × ULN</td>
<td>&gt;2.5-5.0 × ULN</td>
<td>Mild</td>
</tr>
<tr>
<td>2</td>
<td>&gt;2.5-5.0 × ULN</td>
<td>&gt;1.5-3.0 × ULN</td>
<td>≥6-&lt;15 mg/100 ml</td>
<td>&gt;5.0-20.0 × ULN</td>
<td>Decreased portal vein flow</td>
<td>≥2-&lt;3 g/dl</td>
<td>Normal</td>
<td>Normal</td>
<td>&gt;5.0-20.0 × ULN</td>
<td>&gt;5.0-20.0 × ULN</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>&gt;5.0-20.0 × ULN</td>
<td>&gt;3.0-10 × ULN</td>
<td>≥15 mg/100 ml</td>
<td>&gt;20 × ULN</td>
<td>Reversal/retrograde portal vein flow</td>
<td>&lt;2 g/dl</td>
<td>—</td>
<td>—</td>
<td>&gt;20.0 × ULN</td>
<td>&gt;20.0 × ULN</td>
<td>Severe</td>
</tr>
<tr>
<td>4</td>
<td>&gt;20 × ULN</td>
<td>&gt;10 × ULN</td>
<td>≥15 mg/100 ml</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Asterixis</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Life-threatening or disabling</td>
</tr>
</tbody>
</table>

Note: Grade hepatic enlargement only for treatment-related adverse event including VOD.

VOD = veno-occlusive disease; WNL = within normal limits; ULN = upper limit of normal; LLN = lower limit of normal.
high doses used in autologous bone marrow transplantation (BMT) [24, 25].

Chlorambucil, also a nitrogen mustard derivative, was linked to the development of liver damage in six patients from an autopsy series of 181 patients with leukemia or lymphoma [26]. Two patients had postnecrotic cirrhosis, and a third had areas of fibrosis. Variable degrees of centrilobular or periporal liver degeneration and necrosis were seen. Cholestasis was seen, usually in central areas, but occasionally midzonal or periporal in location. All six patients were jaundiced, and chlorambucil was implicated as the principal cause in three. All patients in this series had abnormal liver injury tests. At the time of this 1962 review, there were no specific tests for the various forms of hepatitis, and it can be assumed that many, if not all, of these patients had been transfused. The role of viral infections cannot be excluded and since no similar reports have surfaced, this report can be considered anecdotal. Idiosyncratic hepatotoxicity and a rash developed in another reported case; rechallenge produced the same reaction [27]. This drug must be considered a rare cause of liver dysfunction.

Busulfan is the only drug of the alkylsulfonate class, rarely used now for the myeloproliferative disorders. After administration, the drug is rapidly cleared from the blood, and almost all labeled busulfan is excreted in the urine as methanesulfonic acid. Hepatic metabolism is apparently not important. In standard doses, busulfan rarely causes hepatic dysfunction but has been linked to at least one case of cholestatic hepatitis [28]; another case of cholestasis [29] occurred in a patient in blast crisis who also had leukemic infiltration of the liver.

As a group, the alkylating agents are seldom implicated as hepatotoxins and can be given in the face of altered liver function with relative safety.

Nitrosoureas

The nitrosoureas include carmustine (BCNU), lomustine (CCNU), and streptozotocin. They seem capable of functioning as both alkylating and carbamoylating agents. BCNU depletes hepatic stores of glutathione [30], which may increase the risk of oxidative injury from other sources, such as acetaminophen. BCNU-induced liver abnormalities have been reported in up to 26% of patients [31], from 6 to 127 days following treatment. Elevations of serum aminotransferases, alkaline phosphatase, and/or bilirubin are usually mild and revert to normal over a brief period, although fatalities have been reported; the effects of CCNU are similar [32].

Streptozotocin-induced hepatotoxicity is manifest primarily as a hepatocellular injury pattern and occurs in 15% to 67% of patients [33, 34]. These changes appear a few days to weeks after treatment and rapidly revert to normal without the production of symptoms or the development of chronic changes.

Antimetabolites

The antimetabolites currently in clinical use include cytosine arabinoside (ara-C), 5-fluorouracil (5-FU), 6-mercaptopurine, azathioprine, 6-thioguanine, methotrexate, and gemcitabine. Ara-C is currently the mainstay of treatment of acute myelogenous leukemia and its variants. It differs from the naturally occurring pyrimidine, cytidine, in that arabinoside replaces ribose as the sugar moiety attached to the pyrimidine base. Intracellularly, ara-C is metabolized in three successive phosphorylation reactions to the triphosphate derivative ara-CTP, which inhibits DNA synthesis both by inhibition of DNA polymerase and misincorporation into the DNA molecule. Its effects are thus limited to cells actively synthesizing DNA.

In an early series using ara-C, abnormal liver function tests were reported in 37 of 85 leukemic patients [35], but many had liver function abnormalities prior to treatment, confounding factors such as sepsis or hemolysis, or resolution of biochemical abnormalities despite continuation of therapy. No definite evidence of hepatotoxicity could be found. Ever since, establishing the drug as a hepatotoxin has been especially difficult, since leukemic patients have frequently received transfusions, are subject to infections, are on multiple medications, and are not candidates for liver biopsy because of their usual thrombocytopenia. In patients in whom biopsies have been possible, drug-induced cholestasis has been demonstrated [36, 37]. Although 24 of 27 leukemic patients given high-dose ara-C by continuous infusion over 72 hours developed abnormal liver function tests [38], the effects are reversible and not dose-limiting [38-40].

5-FU is used in the treatment of breast cancer, head and neck cancer, and gastrointestinal cancers. When given intravenously, 5-FU is metabolized by anabolism in tissues to its active form, 5-fluoro-deoxyuridine-monophosphate, which inhibits thymidylate synthetase. The drug is also catabolized, primarily in the liver, as dihydroauracil dehydrogenase reduces the pyrimidine ring. The reduced compound is then cleaved to α-fluoro-β-alanine, ammonia, urea, and carbon dioxide, as in the degradation of uracil. Both the toxicity and the antitumor effect are potentiated if catabolism is blocked by dihydroauracil dehydrogenase inhibition. Approximately 15% of the administered drug is excreted in the urine unchanged. Although the liver plays a key role in its catabolism, 5-FU has not been reported to cause liver damage when given orally, and only rare reports of possible hepatotoxicity have been noted when the drug is given intravenously [41].

When the 5-FU metabolite fluorodeoxyuridine (FUDR, floxuridine) is given intra-arterially by implantable pump for hepatic metastases from colorectal carcinoma, new toxicities become apparent [42]. There are two major pictures:
A) hepatocellular injury with rises in aminotransferases, alkaline phosphatase, and serum bilirubin, and B) stricture of the intrahepatic or extrahepatic bile ducts, accompanied by elevated alkaline phosphatase and bilirubin levels [43-45]. Toxicity appears to be both time- and dose-dependent. With rare exceptions, the hepatitis picture usually improves with the temporary cessation of chemotherapy, but the development of secondary sclerosing cholangitis is irreversible [46, 47]. Two patterns of sclerosis may be seen: a diffuse pattern and the diffuse pattern plus short segments of tight stricture, usually located in the proximal bile ducts [48]. Compared with conventional intravenous 5-FU therapy, intra-arterial FUDR offers a higher response rate, but at the cost of increased liver toxicity [49, 50].

The purine analogue 6-mercaptopurine (6-MP) is used chiefly in the maintenance therapy of acute lymphocytic leukemia. When activated by hypoxanthine guanine phosphoribosyl transferase to the monophosphate nucleotide, the drug inhibits de novo purine synthesis. Phosphorylation to the triphosphate permits incorporation into DNA. The drug is metabolized by xanthine oxidase to 6-thiouric acid.

Hepatotoxicity induced by 6-MP may occur in a variety of settings, especially when the dose of the drug exceeds the usual adult daily dose of 2 mg/kg (6-MP doses in children are prescribed on a mg/m² basis), and may present as either hepatocellular or cholestatic liver disease [51, 52]. Preclinical animal studies noted the development of hepatic necrosis in mice and rats [53], and shortly after its introduction, 6-MP was incriminated in the development of jaundice [54]. Biopsy revealed bland cholestasis, with minimal hepatic necrosis but significant cytologic atypia and disorganized hepatic cords [55], a picture confirmed on multiple occasions [56]. Stopping the drug was followed by resolution of the jaundice.

6-MP may also produce a hepatocellular injury pattern [52]. Serum bilirubin levels are usually between 3 and 7 mg/dl, with moderate elevations in aminotransferases and alkaline phosphatase. Most episodes of jaundice occur more than 30 days after the initiation of therapy. Changing the route of administration from oral to intravenous did not alter the production of hepatotoxicity, as 14 of 40 patients developed aspartate administration (AST) or alanine aminotransferase (ALT) values above 150 U/l [57]. It has been suggested that there is a direct toxic effect of the drug, because rechallenge after discontinuation of the drug does not necessarily shorten the latent period, and systemic manifestations of hypersensitivity such as rash, arthralgias, and eosinophilia are not usually present [52]. However, in a series of 396 patients treated an average of 60 months with 1.5 mg/kg/day of 6-MP for refractory inflammatory bowel disease, hepatitis occurred in only one patient, and liver biopsy suggested hypersensitivity [58].

Azathioprine (AZ), the nitroimidazole derivative of 6-MP, is used for the prevention of solid organ transplant rejection and in the management of patients with autoimmune diseases such as autoimmune hepatitis and inflammatory bowel disease [59]. Like 6-MP, AZ may induce liver toxicity, but with less frequency. Hepatotoxicity is seen chemically as increased serum bilirubin and alkaline phosphatase levels with moderate elevations in aminotransferases and histologically as cholestasis with variable parenchymal cell necrosis.

Most reports of AZ hepatic toxicity have been in the renal transplant population, which has a high incidence of viral hepatitis, causing some observers to doubt the hepatotoxic potential of AZ. In some renal transplant patients, liver abnormalities progressed when AZ was stopped; in others, they improved even though the drug was continued or the patient was rechallenged. A prospective study of patients with psoriasis who were receiving AZ did not show deterioration of liver function [60]. AZ is probably hepatotoxic, but compared with 6-MP, its effects are less frequent, milder, and less dose-dependent. It has been speculated that patients who develop hepatotoxicity are those who convert AZ into 6-MP at an unusually rapid rate [14], an example of host metabolic idiosyncrasy. There is a report of AZ toxicity documented by both histopathology and rechallenge [61]. A patient receiving high doses of AZ for an autoimmune neurologic disorder developed rapidly progressive and fatal sclerosing hepatitis [62].

6-thioguanine, another antipurine, has been implicated in the production of hepatic veno-occlusive disease (VOD) [63-66] and in a single case of peliosis hepatis [67]. An early report [68] described jaundice among the adverse reactions.

The folic acid analogue, MTX, is often a component of combination chemotherapy programs for breast cancer, head and neck cancer, gestational trophoblastic disease, acute lymphoblastic leukemia, and non-Hodgkin’s lymphomas. In high doses, it is a key component of therapy for osteosarcoma. It is also used to treat a variety of nonmalignant diseases, including psoriasis, rheumatoid arthritis (RA), and inflammatory bowel disease.

MTX binds tightly to dihydrofolate reductase, blocking the reduction of dihydrofolate to its active form, tetrahydrofolic acid. Tetrahydrofolic acid is essential for the one carbon transfer reactions required for the synthesis of thymidylate, a precursor to DNA, and the purines adenosine and guanosine, precursors of both DNA and RNA. In standard doses, MTX is excreted unchanged in the urine. In high doses, it is partially metabolized by the liver to 7-hydroxymethotrexate [69]. When used in high doses with leucovorin rescue, MTX diffuses into both normal and malignant cells. Leucovorin enters normal cells, blocking the effects of MTX.
When MTX was used for maintenance therapy in children with acute leukemia, it led to the development of hepatic cirrhosis and fibrosis [70-72]. Fatty change, focal hepatitis, or portal fibrosis in previously untreated patients made the evaluation of MTX’s role in the production of hepatotoxicity difficult.

Elevations of aminotransferases and serum lactate dehydrogenase (LDH) are quite common following high-dose MTX therapy, with an incidence of 14.1% in one report of treatment of gestational trophoblastic disease [73]. The enzymes rise with each course and are higher in patients treated with a daily schedule than in those treated on an intermittent schedule. These abnormalities resolve within one month after the cessation of therapy. High-dose MTX therapy results in acute aminotransferase elevation that is transient, reversible, and, at least in children, does not result in chronic liver disease [74].

Patients with RA or psoriasis who received cumulative doses of less than 2 g of MTX had a low incidence of hepatotoxicity, even though the average duration of therapy ranged from 28 to 48 months [75-78]. In summary, chronic low-dose MTX may lead to fibrosis/cirrhosis, while high-dose may cause altered liver function tests.

There are two case reports of the development of hepatocellular carcinoma following MTX-induced fibrosis: in a child with acute lymphoblastic leukemia and a patient heterozygous for α-1 antitrypsin deficiency, raising the additional question of long-term carcinogenesis with the use of this agent [79, 80].

Gemcitabine is a nucleoside analogue that exhibits cell cycle-dependent and S-phase-specific cytotoxicity, probably due to inhibition of DNA synthesis. It is used for a number of solid tumors, such as pancreatic, breast, and lung cancers. It commonly causes transient rises in transaminases [81], but these are seldom of clinical significance, and dose modification is seldom necessary.

**ANTITUMOR ANTIBIOTICS**

The antitumor antibiotics include doxorubicin, daunorubicin, mitoxantrone, bleomycin, mitomycin, mitramycin (plicamycin), and dactinomycin. Doxorubicin, an anthracycline antibiotic, acts through DNA intercalation, alteration of membrane function, and free radical formation [10]. It is extensively metabolized in the liver, and liver antioxidant capacity, including that provided by glutathione production, may protect against free radical injury [30]. Benjamin [82] 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 [83], 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 anthraquinone antibiotic, may have a lower incidence of serious toxicities than other anthraccline anticancer drugs [84]. When used in leukemic patients, the drug has produced transient elevations in AST and ALT levels [85].

Bleomycin is composed of several polypeptides 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 [86].

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 [87]. 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 [88].

Plicamycin (mithramycin) is the most hepatotoxic chemotherapeutic agent commercially available [89, 90]. 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.
Liver biopsy shows centrilobular hepatocellular necrosis. Coagulation factors II, V, VII, and X, some of which are synthesized by the liver, are depressed.

Since the drug may produce significant thrombocytopenia, the combination may result in an unusual bleeding diathesis. The toxicity can be reduced by a reduction in drug dose. Changing the administration of the drug to an alternate-day schedule decreases toxicity and, in animal studies, was more effective [91]. A review of patients treated with low-dose plicamycin for hypercalcemia revealed a 16% incidence of mild reversible hepatic dysfunction [92].

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 chemotherapy 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 [93]. 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 [94]. The United Kingdom Children’s Cancer Study Group’s Wilms’ Tumor Trial also reported hepatotoxicity associated with pulsed dactinomycin [95]. VOD is discussed below.

**SPINDLE INHIBITORS**

The spindle inhibitor vincristine is excreted primarily by the liver but has seldom been implicated as a hepatotoxin. It has produced hepatotoxicity when used in combination with radiation (see below). Transient aminotransferase elevations, confirmed on rechallenge, have also been reported in a single case [96]. Alkaline phosphatase elevations predict delayed clearance of vincristine and may lead to increased neurotoxicity [97].

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 (see below). 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 [98].

**TOPOISOMERASE INHIBITORS**

Etoposide (VP 16-213), a topoiso-merase II inhibitor, is excreted primarily in the bile but is not usually considered hepatotoxic at standard doses [99]. A recent report, however, identified three patients who experienced severe hepatocellular injury at standard doses [100]. At high doses, etoposide has induced hyperbilirubinemia, elevated aminotransferases, and elevated alkaline phosphatase activity approximately three weeks after administration [101, 102]. These cleared over 12 weeks without sequelae. Elevated serum bilirubin levels have been correlated with subsequent leukopenia [103].

There are two topoisomerase I inhibitors currently available, irinotecan (CPT-11, Camptosar) and topotecan (Hycamptin). 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 [104]. 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 [105]. 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 [106], but minor AST elevations are not uncommon [107]. At high doses, it has been reported to produce abnormal liver tests, especially AST and ALT [108]. The authors suggested that 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 [109]. A case of autopsy-documented hepatic VOD has been reported in a patient who received high-dose carboplatin and etoposide [110]. Although multiple other medications were given as well, the potential role of carboplatin in the production of liver disease deserves mention.

**MISCELLANEOUS AGENTS**

*Escherichia coli* L-asparaginase (L-Asp) hydrolyzes L-asparagine in serum. Depletion of this nonessential amino acid results in death of acute lymphoblastic leukemia cells, which cannot synthesize it. Hepatic toxicity is quite frequent with L-Asp. The mechanism is uncertain, but probably involves impaired protein synthesis from asparagine depletion. Liver steatosis, likely from decreased lipoprotein synthesis, is found at autopsy in 42% to 87% of patients [111-113]. Decreased serum levels of albumin, ceruloplasmin, haptoglobin, transferrin, and γ-globulins, as well as
decreased levels of coagulation factors II, VII, IX, X, and fibrinogen are common [112]. The partial thromboplastin time rises progressively. Moderate elevations of aminotransferase, bilirubin, and alkaline phosphatase also occur. Hyperammonemia may occur as asparagine is broken down. These common changes with L-Asp are usually mild and reversible. Pegasparagase is a polyethylene glycol-linked enzyme which has less immunogenicity, a slower metabolism, and a longer half-life. Its toxicity profile is similar to that of L-Asp, with the potential for elevated liver enzymes and coagulopathy [114].

Procarbazine, initially synthesized as a monoamine oxidase inhibitor, was later found to have activity in Hodgkin’s disease, non-Hodgkin’s lymphomas, small-cell lung cancer, and melanoma. The drug is well absorbed orally and partially excreted in the urine. Most of the drug is rapidly converted to azo-procarbazine by erythrocyte and hepatic microsomal enzymes. From this point on, its metabolism is not clearly defined, and several possible pathways exist. Modification of the dosage in the face of hepatic dysfunction is probably advisable [115]. Procarbazine has been implicated as a cause of granulomatous hepatitis [116].

Hydroxyurea was noted to produce liver toxicity that was not further characterized in one patient in a phase I study, with no mention of hepatotoxicity since [117]. One case report describes hydroxyurea-induced hypersensitivity hepatitis with recurrence upon rechallenge [118]. A review article [13] lists hydroxyurea as a cause for peliosis hepatis, but the original citation is not given.

There have been several reports of hepatic vascular toxicity in melanoma patients treated with single-agent dacarbazine (DTIC) [119-122]. Clinical findings include acute hepatic failure, shock, and death within a few days after the onset of the syndrome [119]. Pathologically, the process involves small and medium-sized veins, but unlike classic nonthrombotic VOD, acute thrombotic occlusions are seen. Eosinophilia and eosinophilic infiltrates are frequently present, suggesting an allergic idiosyncratic mechanism [119, 120]. Such toxicity may be more frequent than commonly thought. DTIC is metabolized by the hepatic microsomal pathway, and it has been suggested that patients with abnormal liver function may be at increased risk for hematologic toxicity [11].

**Biologic Response Modifiers**

Recombinant α-interferon is used in the treatment of hairy cell leukemia, multiple myeloma, non-Hodgkin’s lymphomas, AIDS-related Kaposi’s sarcoma, and myeloproliferative disorders. Its use is often accompanied by an increase in aminotransferases, which clears with discontinuation of therapy [121-124]. At high doses (>10 million units daily), hepatotoxicity may be dose-limiting [125, 126]. At lower doses, the drug is used to treat chronic viral hepatitis. The only evident hepatotoxicity in this population is the exacerbation of unrecognized autoimmune hepatitis [124, 127].

Interleukin 2 (IL-2) is used in the therapy of renal cell carcinoma and melanoma. Many patients undergoing therapy with IL-2 experience elevations of serum bilirubin in the 2 to 7 mg/dl range due to intrahepatic cholestasis [128]. Elevations of AST, ALT, and alkaline phosphatase and hypoalbuminemia and prolonged prothrombin times are also frequent. IL-2 activates Kupffer cells and induces leukocyte and platelet adhesion to hepatic sinusoidal endothelium, with subsequent impaired sinusoidal perfusion and hypoxic damage [129]. Reversal usually occurs within several days after the cessation of therapy.

**Hormones**

Although many new agents are now available, androgens are still used in the hormonal manipulation of breast cancer and carry the risk of intrahepatic cholestasis [130]. The chronic use of any 17-alkyl androgen has the potential for the development of hepatic adenocarcinomas [131, 132].

Cholestatic hepatitis, likely idiosyncratic, has been reported following the use of the antiandrogen flutamide for prostate cancer [133] and megestrol acetate [134] and tamoxifen therapy for breast cancer [135].

**Hepatic VOD**

BMT, which commonly uses very high doses of chemotherapeutic agents, total body irradiation, and combination chemotherapy may result in hepatotoxicity. VOD is a nonthrombotic obliteration of small intrahepatic veins by subendothelial fibrin [136], associated with congestion and potentially fatal necrosis of centrilobular hepatocytes. It frequently occurs in the setting of BMT [137]. The presenting symptoms of VOD are painful hepatomegaly, rapidly accumulating ascites or unexplained weight gain, and bilirubin ≥2 mg/dl within 20 days of BMT [138]. The resultant vascular engorgement causes hepatomegaly and ascites. If the acute phase does not reverse, the veins undergo progressive fibrosis, and atrophy of centrilobular hepatocytes occurs [136]. Therapy is largely supportive and consists mainly of salt and fluid restriction. In most large BMT series, the incidence is 10%-20% [136, 138], with mortality ranging from 7%-50%.

Although there are risk factors besides the conditioning regimen [134], the chemotherapeutic agents involved in VOD have included alkylating agents, antimetabolites, and various combinations, typically drugs that undergo some sort of hepatic metabolism [136, 139-143]. High-dose cyclophosphamide chemotherapy, alone or with other
agents in preparation for BMT, has caused hepatic VOD [136, 144].

Busulfan at doses of 16 mg/kg or higher may produce hepatic VOD in about 20% of adult patients and up to 5% of children undergoing BMT [141, 145]. Busulfan clearance occurs more rapidly in children than adults, accounting for the difference in rates [146]. Dimethyl busulfan is also frequently implicated [147].

In the setting of BMT, graft-versus-host disease may be associated with VOD, but most cases of VOD are likely drug-induced. Although occasionally seen with single-agent DTIC [118-122, 148-150], 6-thioguanine [63], following renal transplantation and AZ therapy [151] or following ABVD (doxorubicin [Adriamycin], bleomycin, vinblastine, dacarbazine) chemotherapy for Hodgkin’s disease [152, 153], most cases of VOD have followed high-dose chemotherapy in preparation for BMT [154-158]. VOD associated with 6-thioguanine may be reversible upon discontinuation of the drug [63, 64]. Indeed, such hepatotoxicity may be the dose-limiting toxicity of preparatory regimens for BMT [144]. Thus, less toxic regimens or agents that could prevent VOD are needed. In regard to the latter, pretreatment with glutathione has been reported to protect the liver in an animal model treated with high doses of alkylating agents [159].

A syndrome of hepatopathy-thrombocytopenia (HTS) consistent with VOD has also been reported in Wilms’ patients [160]. HTS was noted in 5 of 355 (1.4%) patients treated with combination chemotherapy but was not seen in 146 patients who received only vincristine. The syndrome occurred within 10 weeks of diagnosis, lasted an average of 12 days, and resolved with supportive therapy. Approximately 3% of patients who receive the combination of vincristine and actinomycin D develop hepatomegaly, elevated serum enzymes, hyperbilirubinemia, and ascites, thus producing a syndrome resembling hepatic VOD [161]. This effect was seen in unirradiated children, with or without nephrectomy.

**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 [162]. 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 hyperplasia (NRH), was observed in patients with chronic granulocytic leukemia treated with the combination of busulfan and 6-thioguanine [163]. 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 VOD, the initiating injury is believed to be vascular, in this case to the portal vein branches [164].

When high doses of both BCNU and etoposide were used to treat high-grade gliomas [165], 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 [166]. 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 [167]. 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 [168].

Adjuvant chemotherapy for breast cancer with cyclophosphamide, MTX, and 5-FU has produced both abnormal liver tests and focal defects on radionuclide scans [169]. 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 [170]. 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 florafur, doxorubicin, and cyclophosphamide [171]. In this setting, liver biopsy may be necessary to exclude tumor metastases and confirm the impression of drug-induced changes.

Hepar lobatum, previously seen almost exclusively with healed or tertiary syphilis, has also been described in association with combination chemotherapy for breast cancer [172].

While the addition of 5-ido-2′ deoxyuridine to 5-FU did not increase hepatotoxicity, the addition of leucovorin...
produced greater toxicity than FUDR alone [173]. 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 [174]. The combination of N-hosphonacetyl-aspartate and 5-FU caused transient hepatic abnormalities in 15 of 17 patients, with ascites, hyperbilirubinemia, and hypoalbuminemia [175].

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 [176]. 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 [177]. 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 (A.S. Glicksman and H.W. Grunwald, personal communication). The radiation encompassed the entire liver to total doses of 1,500 to 2,500 rads and was given with monthly vincristine. Ten of 35 patients developed severe toxicity (AST greater than three times normal, clinical evidence of liver failure), and there was a death from hepatitis and thrombocytopenia. Another nine patients had moderate toxicity. The investigators postulated that radiation delayed the transit of vincristine through the liver and its excretion into bile. 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 [178]. A similar phenomenon has been described with radiation and doxorubicin [179] or radiation alone [180].

Many drugs without antineoplastic effects may cause hepatotoxicity. Intensive chemotherapy has been implicated in the development of fatal hepatic necrosis following haloalkane anesthesia [181]. Allopurinol, commonly given with chemotherapy to prevent uric acid nephropathy and secondary gout, has also been linked to fulminant hepatic

| Table 2. Chemotherapy dose modification in liver disease |
|---------------------------------|-----------------|---------------|---------------|
| Agent                           | Bilirubin       | Aminotransferases | Alk phos | % Dose administered | Reference |
| Cyclophosphamide                | No dose reduction | Any            | ALT or AST 2-3 x ULN | 75% | [81] |
| Cytarabine                      | Any             | ALT or AST >3 x ULN | 50% | |
| Daunorubcin                     | >85 µM          | AST >180       | 75% | [195] |
| Doxorubicin                     | 20-51 µM        | ALT or AST 2-3 x ULN | 50% | |
| Etoposide                       | 25-51 µM        | ALT or AST >3 x ULN | 25% | |
| Daunorubicin                    | 20-51 µM        | >85 µM         | 0% | |
| Daunorubicin                    | 51-85 µM        | >85 µM         | 0% | |
| Daunorubicin                    | >85 µM          | Elevated       | 50% | [196] |
| 5-FU                            | >85 µM          | ALT or AST >180 | 0% | |
| Vincristine                     | >85 µM          | ALT or AST >180 | 0% | No dose reduction |
| Procarbazine                    | >85 µM          | ALT or AST 2 x ULN | 75% | [197] |
| Gemcitabine                     | >85 µM          | ALT or AST >180 | 40% | No dose reduction |
| Bleomycin                       | >85 µM          | ALT or AST 2 x ULN | 25% | No dose reduction |
| cisplatin                       | >85 µM          | ALT or AST >180 | 0% | No dose reduction |
| Mitomycin                       | >85 µM          | ALT or AST >180 | 0% | No dose reduction |
| Paclitaxel                      | <1.5 mg/dl      | ALT or AST 2 x ULN | 75% | [182] |
| Paclitaxel                      | 1.5-30 mg/dl    | <1.5 x ULN | 40% | |
| Paclitaxel                      | >30 mg/dl       | >1.5 x ULN | 25% | |
failure, presumably due to a hypersensitivity reaction [182, 183]. There is also a report of allopurinol hepatotoxicity possibly potentiated by an interaction with tamoxifen [184]. Several cases of fatal, massive hepatic necrosis and others of liver damage have been attributed to ketoconazole [185-187]. 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 [188]. The antiemetic ondansetron has been implicated in hepatocellular injury and jaundice [189]. The current popularity of alternative medicines has led to the recognition of herbal hepatitis [190]. Specific inquiry about such nonstandard agents is particularly important when hepatotoxicity occurs in the outpatient setting. Hepatitis has also been attributed to G-CSF [191], and CSF-secreting tumors may cause paraneoplastic hepatitis [192].

Finally, a syndrome of hyperammonemia has been reported in patients who have received high-dose combination chemotherapy for hematologic neoplasms [193]. 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.

**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. Guidelines on dose modification in hepatic disease are largely empiric (Table 2). The dosing of doxorubicin is an example of such an empiric guideline, but the situation may be much more complex [81, 194]. Clinical judgment and a high index of suspicion remain critical tools in preventing and treating hepatic manifestations of cancer chemotherapy.

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