23

Hepatotoxic Effects of Oncotherapeutic and Immunosuppressive Agents

Chemotherapy for neoplastic disease and chemical immunosuppression involve the use of agents that interfere selectively with metabolic pathways or have other cytotoxic effects; several of these agents are hepatotoxic (1–8). Other agents in the group appear to spare the liver or to produce hepatic injury rarely and as the result of host idiosyncrasy (5). Although abnormal values for biochemical tests are common, clinically significant hepatic injury is relatively uncommon. It seems almost paradoxical that some agents that are potent cell poisons, and that are metabolized by the hepatocyte, produce little or no hepatic damage.

Several factors appear to account for the sparing of the hepatocyte by agents so lethal to the neoplastic cell. These agents exert their toxic effects preferentially on rapidly proliferating tissues, such as those of the bone marrow, gastrointestinal tract, and neoplasms (3). Accordingly, the slowly multiplying hepatic tissue should be relatively unsusceptible (3). Furthermore, the broad range of metabolic activity of hepatocytes may provide opportunity for balance between production and disposition of toxic metabolites; whereas transformation of the drug in the neoplastic cell (e.g., by action of phosphamidase or cyclophosphamide) may convert it to a cytolytic alkylating agent (5). Additionally, administration of anticancer drugs may lead to amplification of the multidrug-resistance gene, which encodes an organic ion transporter (*p*-glycoprotein). Conceivably, this may add protection by enhanced excretion of potentially hepatotoxic drugs (8). Nevertheless, considering the role of alkylation and arylation of cell macromolecules of the hepatocyte in the production of hepatic injury by known hepatotoxins (Chapter 5), the oligotoxicity for the liver of alkylating antineoplastic agents is somewhat surprising.

Also relevant to the hepatotoxic effects of anticancer drugs is the difficulty of identifying any hepatic injury therapy must be distinguished from the effects on the liver of the neoplasm, coincidental viral hepatitis, other infections, other drugs, and total parenteral nutrition.

The number of candidate oncotherapeutic agents studied in experimental animals and tested in patients is far too great, and the data regarding the possible adverse effects of many of them on the liver are too scant, to permit systematic analysis of the hepatotoxicity of cancer chemotherapy. Nevertheless, sufficient information is available to define the effects of some agents on the liver (Table 23.1) and to discern some general principles regarding the relation between the type of agent and the potential for producing hepatic injury.

FORMS OF HEPATIC INJURY

For the most part, the forms of acute (Table 23.2) and chronic (Table 23.3) hepatic injury produced by oncotherapeutic agents are similar to those produced by other agents. Several forms of the injury, however, are particularly prominent. Steatosis is more frequently noted in the hepatic injury of several anticancer agents than in that produced by most other drugs. Steatocirrhosis seen with methotrexate (MTX) therapy but is not seen with most other medicinal hepatic injury. Veno-occlusive disease (VOD), the dramatic lesion characteristically resulting from pyrrolizidine alkaloids, is produced by several oncotherapeutic and immunosuppressive agents, singly and in various combinations (4–6,8–11), and not by other medicinals (Table 23.4). Another unique drug-induced lesion is the sclerosing cholangitis that is seen as a complication of "pump" infusion of floxuridine into the hepatic artery for treatment of metastatic hepatic carcinoma (12–21) (Table 23.5).

Acute Injury

The acute hepatic lesions of cancer chemotherapy are

TABLE 23.1. *Some hepatic lesions produced by agents used in cancer therapy*

Drug	Biochemical pattern of injury	Fat	Necrosis	Cholestasis	VOD	Peliosis
Aclarubicin	AT	–	–	–	–	–
Aminoglutethamide	Cholestatic	–	–	+	–	–
Amsacrine	Hepatocellular/cholestatic	+	+	+	–	–
Anabolic steroid[a]	Cholestatic	–	–	+	–	+
Asparaginase	Hepatocellular	+	+[b]	–	–	–
Azacytidine	Hepatocellular	+	+	–	–	–
Azatepa	Hepatocellular					
Azathioprine	Hepatocellular/cholestatic	+	+	+	+	+
Bacille Calmette-Guérin[c]	Hepatocellular	+	+	–	–	–
Bleomycin	Hepatocellular[b]	+	–	–	–	–
Busulfan[d]	Cholestatic	–	–	+	+[e]	+
Carboplatin	Hepatocellular/cholestatic	+[e]	–	+	+[e]	
Carmustine	Hepatocellular	+	+	–	+	–
Chlorambucil	Hepatocellular	–	+	–	–	–
Chloropurine	Hepatocellular	–	+	–	–	–
Chlorozocin	Hepatocellular/cholestatic	–	+	+	–	–
Cisplatin	Hepatocellular	+	+	+	+[e]	–
Cladribine	None					
Cyclosporine	Cholestatic	–	–	+	–	–
Cyclophosphamide	Hepatocellular	–	+	–	+[e]	–
Cyproterone	Hepatocellular					
Cytarabine	Hepatocellular	–	+	–	+[a]	–
Dacarbazine	Hepatocellular	–	+	–	+	–
Dactinomycin (actinomycin D)[e]	Hepatocellular	+	+	+	+	–
Daunorubicin	Hepatocellular[e]	-	+	–	+[e]	–
Dichloromethotrexate	Hepatocellular	+	+	–	–	–
Diethylstilbestrol	Hepatocellular	+	–	–	–	–
Dimethylbusulfan	Cholestatic	–	–	+	+[a]	–
Doxorubicin	Hepatocellular	–	+	–	+[b]	–
Estramustine	Hepatocellular	–	–	–	–	–
Estrogens (Steroids)	Cholestatic	–	–	+	±	–
Etoposide	Hepatocellular	–	+	–	–	–
Floxuridine[f]	Hepatocellular/cholestatic	±	+	–	–	–
Fluorouracil	AT	–	–	–	–	–
Flutamide	Hepatocellular/cholestatic	–	+	+	–	–
Frentizole	Hepatocellular					
Homoharringtonine	AT					
Hydrazines	Hepatocellular	+	+	–	–	–
Hydroxyprogesterone	Cholestatic	–	–	+	–	+
Hydroxyurea	Hepatocellular	+	–	–	–	+
Idarubicin	AT	–	–	–		–
Ifosfamide	AT					
Indicine-*N*-oxide	Hepatocellular	–	+	–	+	–
Interferons	AT	–	–	–	–	–
Interleukin-2[g]	Cholestatic	+	+	+	–	–
Interleukin-6	Cholestatic	–	±	–	–	–
Lomustine	None	–	–	–	–	–
Maytansine	AT	–	–	–	–	–
Mechlorethamine	None	–	–	–	–	–
Medroxyprogesterone	Cholestatic	–	–	+	–	+
Melphalan	AT	–	–	–	–	–
Mercaptopurine	Hepatocellular/cholestatic	–	+	+	–	–
Methotrexate	Hepatocellular	+	+[h]	–	–	–
Mithramycin	Hepatocellular	–	+	–	–	–
Mitomycin	Hepatocellular	+	–	–	+	–
Mitotane	AT	–	–	–	–	–
Mitoxantrone	AT	–	–	–	–	–
Monomethylformamide	Hepatocellular	+	+	–	–	–
Nilutamide	Hepatocellular	–	+	–	–	–
Pentostatin	Hepatocellular	–	–	–	–	–
Procarbazine	Hepatocellular[i]	–	+	–	–	–
Puromycin	Hepatocellular	+	–	–	–	–
Pseudisocytidine	Hepatocellular					
Semustine	AT	–	–	–	–	–
Streptozocin	Hepatocellular	+	+	–	–	–

TABLE 23.1. *Continued.*

Drug	Biochemical pattern of injury	Fat	Necrosis	Cholestasis	VOD	Peliosis
Tacrolimus	Hepatocellular					
Tamoxifen	Cholestatic/hepatocellular	–	–	+	–	+
Teniposide	Hepatocellular	–	+	–	–	–
Thioguanine	Hepatocellular/cholestatic	–	+	+	+	–
Thiotepa	Hepatocellular	+	+	–	–	–
Trimetrexate	None	–	–	–	–	–
Triethylenemelamine	None	–	–	–	–	–
Uracil mustard	AT					
Urethane	Hepatocellular	–	+	–	+	–
Vinca alkaloids	Hepatocellular	–	+[e,h]	–	+[e]	–

AT, increased aminotransferase levels but no jaundice; +, present ; –, absent; ±, uncertain.
[a] Incriminated in hepatic adenoma and carcinoma.
[b] Hepatic injury is minor component of adverse effects of drug.
[c] Granuloma.
[d] Also incriminated, with other agents, in production of nodular regenerative hyperplasia.
[e] Only when given with other agents or radiotherapy.
[f] Characteristic injury is sclerosing cholangitis when drug is administered by pump into hepatic artery.
[g] Pattern of injury is consistently cholestatic. Histological changes show more variation.
[h] In large parenteral doses.
[i] Rare

TABLE 23.2. *Acute hepatic injury associated with agents used in cancer therapy.*

Cytotoxic	Agents
Necrosis	
Dose-related, relatively frequent	Mithramycin, *N*-methylformamide, mercaptopurine, nitrosoureas, streptozocin, methotrexate[a]
Dose-unrelated, relatively rare	Chlorambucil, cyclophosphamide, cytarabine, cytoproterone, etoposide, flutamide, frentizole, thioguanine
Steatosis	Dactinomycin, asparaginase, bleomycin, methotrexate, mitomycin,[a] puromycin
Steatosis plus necrosis	Asparaginase, cisplatin, methotrexate,[a] thiotepa
Cholestatic	Anabolic steroids, estrogenic steroids, aminogutethamide, azathioprine, amsacrine, busulfan, 4,4′-diaminodiphenylamine, medroxyprogesterone, tamoxifen
Mixed cholestatic-cytotoxic	Chlorozocin, mercaptopurine, thioguanine, azathiopurine

[a] In high dose.

TABLE 23.3. *Chronic hepatic lesions associated with agents used in cancer therapy*

Type of injury	Agents
Cytotoxic injury	
Chronic hepatitis	Azathioprine, doxorubicin
Steatosis	Dactinomycin, asparaginase, glucocortisteroids, methotrexate, mitomycin C, puromycin
Phospholipidosis	amphophilic compounds
Mallory bodies (alcoholic hyaline)	Diethylstilbestrol, tamoxifen
Cirrhosis	
Steatocirrhosis	Methotrexate
Biliary cirrhosis	Azathioprine, floxuridine
Congestive cirrhosis	Drugs that lead to VOD or hepatic thrombosis
Cholestatic lesions	
Chronic intrahepatic cholestasis	Azathioprine
Sclerosing cholangitis	Floxuridine
Vascular lesions	
Peliosis hepatis	Anabolic steroids, azathioprine, medroxyprogesterone, hydroxyurea, tamoxifen, OCs, DES, thioguanine
Hepatic vein thrombosis	Combination therapy (Table 23.18)
Veno-occlusive disease	(Table 23.4)
Granulomas	Many drugs
Neoplasms	
Adenomas	Anabolic steroids, OCs
Carcinoma, hepatocellular	Azathioprine, anabolic steroids, chlorambucil, OCs, DES, methotrexate
Angiosarcoma	Anabolic, OCs, DES
Non-cirrhotic portal hypertension	

TABLE 23.4. *Oncotherapeutic and immunisuppressive agents that can lead to veno-occlusive disease*[a]

Drug	Trade name
Azathioprine	Imuran
Busulfan	Myleran
Carmustine	BCNN, BICNU
Cisplatin	Platinol
Cyclophosphamimide	Cytoxan
Cytarabine	Cyosine arabinoside, ARA-C, Cytosar-U
Dacarbazine	DTIC
Dactinomycin	Actinomycin, Cosmegen
Daunorubicin	Cerubidine
Dimethylbusufan	—
Doxorubicin	Adriamycin
Floxuridine	FUDR
Indicine-*N*-oxide	—
Mechlorethamine	Mustargen
6-Mercaptopurine	Purinethanol
Mitomycin	Mitocin, Mutamycin
Thioguanine	TG
Urethane	Ethyl carbamate
Vincristine	Oncovin
X-Irradiation Combinations	

[a]Alone or in combination with other agents or x-irradiation.

sic hepatotoxins that produce necrosis as a dose-dependent effect. Most produce necrosis relatively rarely as a dose-independent idiosyncratic reaction (6). Acute cholestasis is an uncommon form of anticancer drug injury, although busulfan (23,24), azathioprine (25,26), aminoglutethamide (27,28), amsacrine (6), tamoxifen (29,30), medroxyprogesterone (8), and the obsolete agent, 4,4′-diaminodiphenylamine (6) can cause cholestatic injury.

Chronic Injury

Cytotoxic Lesions

Steatosis is a frequent chronic cytotoxic lesion resulting from several anticancer drugs, especially MTX (6) (Table 23.3). Chronic hepatitis resembling the autoimmune type, a lesion and syndrome that can be produced by several drugs, is not readily ascribable to any of the cancer chemotherapy agents. However, I have seen the lesion as an apparent reaction to azathioprine and in published (31) photomicrographs of doxorubicin-induced injury.

Phospholipidosis, a lesion characterized by phospholipid-engorged lysosomes and produced by a number of amphiphilic drugs (32), has not been recorded as a lesion of oncotherapeutic agents other than the investigational antileukemic drug, AC3579 (33). The Mallory body, a lesion seen in alcoholics and in several other clinical conditions (Chapter 6), is not seen with any of the usual anticancer agents. It has been produced in experimental animals (34) by administration of diethylstilbestrol and in a patient with prostatic carcinoma (35) treated with that drug. Tamoxifen also has been implicated in the development of Mallory bodies (35a,35b). Several types of cirrhosis may occur after anticancer therapy (Table 23.3).

Cholestatic Injury

Chronic intrahepatic cholestasis may follow the acute cholestasis induced by azathioprine (Fig. 23.1). Reference has been made to the striking sclerosing cholangitis (Fig. 23.2) produced by hepatic artery infusion of floxuridine (12–21) in the treatment of metastatic hepatic carcinoma (Table 23.5).

Vascular Lesions

Peliosis Hepatitis. This lesion has been associated in the past with terminal tuberculosis or carcinomatosis (36), more recently with C17-alkylated steroids, and, rarely, with oral contraceptives (Chapter 4). Peliosis hepatis also has been seen in patients (8) taking tamoxifen (37), hydroxyurea (4) thioguanine, medroxyprogesterone acid (8), or azathioprine (4) (Table 23.3).

Hepatic Vein Thrombosis. The drugs most associated with hepatic vein thrombosis are the oral contraceptives (38). Cancer chemotherapy is rarely the cause of the injury, but the lesion has been reported as a complication of chemotherapy for Hodgkin's disease (39) and administration of dacarbazine (DTIC) (40).

TABLE 23.5. *Published reports of sclerosing cholangitis occurring as a complication of pump infusion of floxuridine into the hepatic artery*

Authors	No. cases	Incidence of lesion (%)	Year	Ref no.
Anderson et al.	20	40	1986	16
Bolton et al.	2	33[a]	1985	13
Botet et al.	6	7	1985	14
Doria et al.	8	100[b]	1986	18
Hermann et al.	20	100	1987	19
Hohn et al.[c]	31	56	1986	12
Kemeny et al.	8	17	1985	15
Ludwig et al.	1	—	1989	20
Shea et al.[c]	17	100	1986	17

[a]Reflects authors' estimate that "one-third" of treated patients develop the lesion.
[b]Reflects all of patients studied.
[c]The two reports are from the same institution and figures may overlap.

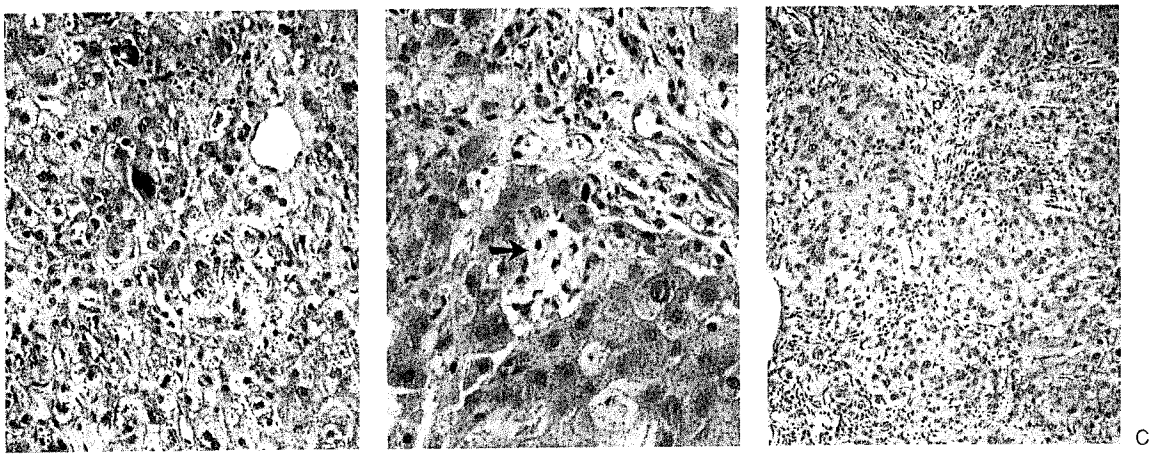

FIG 23.1. Liver biopsy from a patient who developed chronic cholestasis (vanishing bile duct syndrome) after taking azathioprine for many months. Jaundice had been present for 11 months at that time of the biopsy. **A:** Note cholestasis with huge bile casts in canaliculus. **B:** Cholate stasis (*arrow*) reflected by foamy striated cells. **C:** Portal areas (P) showing fibrosis and lack of bile ducts.

Veno-Occlusive Disease. This lesion leads to morphologic changes and a syndrome resembling that of hepatic vein thrombosis, namely the Budd-Chiari syndrome (41). In VOD, however, the lesion is fibrotic and involves partial or complete obliteration of the lumina of the efferent venules rather than thrombotic occlusion of the hepatic veins (41). The lesion is typical of pyrrolizidine alkaloid toxicity, which is the most common cause of the entity worldwide (9,41,42). In this country the most common causes are anticancer and immunosuppressive drugs (22,43–49) and radiation injury (50) of the liver. It is relatively common in patients receiving chemotherapy or immunosuppressive therapy, particularly in recipients of bone marrow transplants (11). VOD develops in 10% to 60% of patients during the first few weeks after bone marrow transplantation (4,6,9–11,43–49). Superb exposition of the VOD that is associated with bone marrow transplantation is continued in the writing of Jones et al. (9), McDonald et al. (10), and Bearmen (11). It is characterized by partial or complete fibrotic occlusion of terminal hepatic venules (central veins) with congestion and necrosis of the perivenous area (zone 3). The diagnosis should be suspected when abdominal swelling and increased aminotransferase levels develop during or after

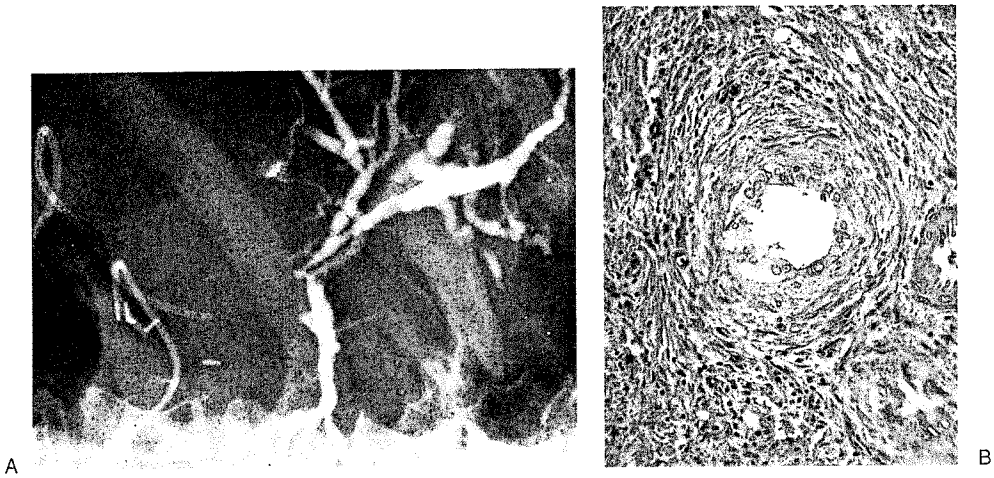

FIG. 23.2. A: Retrograde cholangiogram showing sclerosing cholangitis in a patient after 6 months of pump infusion therapy with floxuridine. (Courtesy of Dr. Paul Shorb, George Washington University Med-

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