Chemotherapy Dosing in the Setting of Liver Dysfunction

By John W. Eklund, MD and Mary F. Mulcahy, MD

Advanced cancer in the setting of liver dysfunction poses a dilemma for physicians, as many cancer chemotherapeutic agents undergo hepatic metabolism. Most cytotoxic drugs have a narrow therapeutic index, and the administration of chemotherapy to patients with liver impairment results in complicated safety issues. We present a concise review of cancer chemotherapy dosing in the setting of liver dysfunction. Although caution in treating all patients with hepatic failure is essential, the use of certain agents provokes greater concern than others. Continuous-infusion fluorouracil, capecitabine (Xeloda), mechlorethamine (Mustargen), cyclophosphamide, topotecan (Hycamtin), and oxaliplatin (Eloxatin) appear to be relatively well tolerated. On the contrary, taxanes, vinca alkaloids, irinotecan (Camptosar), and anthracyclines may cause unacceptable toxicity if administered to patients with poor hepatic function. For many anticancer agents, the paucity of data prohibits formal dosing recommendations, and most guidelines remain empiric.

The administration of chemotherapy to cancer patients with hepatic dysfunction requires careful consideration. There are a variety of ways in which liver impairment affects drug kinetics, including changing the intrinsic hepatic clearance of drugs, reducing hepatic metabolic capacity, and altering the biliary excretion of drugs. In addition, low serum albumin levels lead to increased fractions of free drug, and portal hypertension can affect drug absorption.

Unfortunately, most clinical trials exclude patients with impaired hepatic function; much of what is known about individual chemotherapeutic agents in the setting of liver failure is based on small, retrospective studies. Very few agents have undergone formal phase I testing in liver dysfunction cohorts, and empirical guidelines are frequently used in clinical practice. Furthermore, there is no standardized system with which to define liver dysfunction in patients with cancer. The serum total bilirubin level is the marker most commonly used to assess the need for chemotherapy dose adjustments, but this represents an oversimplified strategy. To further complicate issues, various sources often differ in dosing recommendations, with no consensus. Thus, there are many potential hazards involving the administration of cancer chemotherapy to patients with impaired hepatic function.

Two review articles published in 1992 by Perry and Koren et al and a subsequent article in 1998 by Donelli et al[3] have provided important guidelines for the use of chemotherapy with liver dysfunction. Since 1998, there have been a number of important new findings, particularly regarding irinotecan (Camptosar), fluorouracil (5-FU), capecitabine (Xeloda), gemcitabine (Gemzar), paclitaxel, and oxaliplatin (Eloxatin) in patients with impaired hepatic function. Patients with gastrointestinal malignancies may benefit from these agents; however, the high incidence of hepatic metastases, often accompanied by liver function test abnormalities, precludes their use. We have compiled the results of these newest findings and have highlighted pertinent recommendations from past reviews.

Fluoropyrimidines

Hepatic metabolism is the major route of elimination of 5-FU. Dihydropyrimidine dehydrogenase (DPD) is the initial, rate-limiting enzyme in 5-FU catabolism. In addition to being present in the liver, DPD is also found in the gastrointestinal tract and in tissues throughout the body. Early reports described significant toxicity when full-dose bolus 5-FU was administered to patients with liver metastases and jaundice, leading to the recommendation that 5-FU be withheld in patients with serum bilirubin concentrations greater than 5 mg/dL.[4]

A phase I study evaluated infusional 5-FU in cancer patients with organ dysfunction.[5] A total of 64 patients were divided into three cohorts. The first cohort had renal insufficiency (serum creatinine: 1.5-3.0 mg/dL) but normal total bilirubin levels. The second cohort had normal renal function but mild-to-moderate hepatic dysfunction with total bilirubin levels of 1.5 to 5.0 mg/dL. The third cohort had normal renal function and moderate-to-severe hepatic dysfunction with total bilirubin levels greater than 5.0 mg/dL. In all cohorts, patients were safely treated with 5-FU (2,600 mg/m²)
administered as a continuous intravenous infusion over 24 hours along with leucovorin (500 mg/m²) on a weekly schedule. There was no relationship between serum bilirubin and 5-FU clearance, and toxicity did not appear to correspond to organ dysfunction.

Capecitabine is an oral prodrug that is metabolized to 5-FU and has clinical activity that mimics infusional 5-FU. Capecitabine is readily absorbed from the gastrointestinal tract and activated, through a series of enzymatic reactions occurring first in the liver and subsequently in most tissues (including tumor tissue), to the active drug 5-FU. It is catabolized by DPD as described above.

A study of 14 patients with normal liver function and 13 patients with liver function test abnormalities due to liver metastases demonstrated no clinically significant influence on the pharmacokinetic parameters of capecitabine or its metabolites in the setting of hepatic dysfunction (mean bilirubin: 6.5 mg/dL, range: 0.9-28.3 mg/dL).[6]

In a separate report, a woman with metastatic breast cancer and severe liver dysfunction (total bilirubin: 12 mg/dL) achieved a partial response after seven cycles of capecitabine at 2,500 mg/m²/d in two divided doses for 2 weeks followed by 1 week of rest.[7] The treatment was well tolerated, with National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade 2 hand-foot syndrome and mild nausea being the only side effects. Based on these reports, capecitabine can be considered for patients with liver dysfunction.

**Gemcitabine**

Gemcitabine (Gemzar) is inactivated by cytidine deaminase to an inactive metabolite, which is primarily eliminated in the kidney. A phase I study of gemcitabine found that patients with serum aspartate aminotransferase (AST) elevation greater than two times normal, but with normal bilirubin levels, tolerated gemcitabine well without a need for dose reduction.[8] In contrast, patients with elevated total bilirubin levels (median: 2.7 mg/dL, range: 1.7-5.7 mg/dL) had a significant deterioration in liver function with the administration of gemcitabine.

Of 8 patients, 3 developed doselimiting toxicity (DLT) at a dose of 800 mg/m²; 8 of 10 developed DLT at a dose of 950 mg/m². Further hyperbilirubinemia and elevated transaminases were the most common DLTs. The deterioration in liver function was transient, often lasting less than 1 week. There were no apparent pharmacokinetic differences compared with historical controls. The authors concluded that patients with elevated bilirubin levels should initially be treated with a weekly gemcitabine dose of 800 mg/m², and subsequently escalated doses if the therapy is tolerated.

**Irinotecan**

Irinotecan (Camptosar) is mainly eliminated by the liver and, to a lesser extent, by the kidneys. Irinotecan's active metabolite, SN-38, is glucuronidated by the hepatic enzymes uridine diphosphate glucuronosyltransferases. Severe neutropenia and diarrhea have been reported in patients with Gilbert's disease.[9] Certain genetic variants in the UDP-glucuronosyltransferase 1A1 (UGT1A1) gene predict the risk of severe neutropenia from irinotecan.[10]

A phase I study has been conducted administering irinotecan on an every-3-week schedule to patients with varying degrees of liver dysfunction.[11] High bilirubin and alkaline phosphatase levels were associated with an exponential decrease in the clearance of irinotecan, and drug toxicity correlated with serum bilirubin concentration. Patients with total bilirubin levels less than 1.5 times the upper limit of normal (ULN) tolerated full-dose therapy (350 mg/m² every 3 weeks). The maximum tolerated dose for patients with total bilirubin levels 1.5 to 3.0 times the ULN was 200 mg/m² every 3 weeks. One of five patients developed DLT at this dose. Three of six patients with bilirubin levels 1.5 to 3.0 times the ULN developed DLT at a dose of 240 mg/m². Three patients with bilirubin levels greater than three times the ULN (range: 3.6-5.8 times the ULN) were treated with one cycle of irinotecan at a dose of 100 mg/m². Although none of the three patients developed DLT, most experienced rapid hepatic tumor progression associated with aggravation of liver dysfunction and worsening of performance status. Therefore, no dosing recommendations could be made for patients with serum bilirubin levels greater than three times the ULN. The most common DLTs in patients with hyperbilirubinemia were NCICTC grade 4 febrile neutropenia and diarrhea.

A separate phase I study confirmed that irinotecan dose reductions are required in patients with liver impairment.[12] Twelve patients with hyperbilirubinemia (median serum bilirubin: 2.1 mg/dL, range: 1.0-5.5 mg/dL) were given irinotecan on an every-3-week schedule. Three of five patients developed DLT at a dose of 145 mg/m², and zero of seven patients developed DLT at a dose of 115 mg/m². Two of the DLTs were neutropenia and one was worsening liver function. There were no episodes of dose-limiting diarrhea in patients with an increased bilirubin level. This is consistent with the
hypothesis that biliary excretion of SN-38 is responsible for the diarrhea. The authors conclude that patients with elevated bilirubin treated with irinotecan have an increased risk of toxicity; a dose reduction is recommended.

**Topotecan**

Topotecan (Hycamtin) pharmacokinetics exhibit significant interpatient variation. It is metabolized via pH-dependent hydrolysis of its lactone moiety, with minor metabolic pathways involving glucuronidation and the hepatic enzyme CYP3A. Topotecan has been studied in patients with impaired hepatic function.\[13\] Twentyone patients were enrolled: 7 control patients with normal hepatic function (serum bilirubin: < 1.2 mg/dL) and 14 patients with liver dysfunction (mean serum bilirubin: 4.3 mg/dL, range: 1.7-14.9 mg/dL). Patients were treated with intravenous topotecan at doses of 0.5, 1.0, or 1.5 mg/m$^2$ daily for 5 consecutive days. Most patients received more than one course of treatment.

No pharmacokinetic or pharmacodynamic alterations were found in patients with impaired liver function when compared with the control group. In addition, the nature and severity of treatment-induced toxic effects were similar in patients with and without liver injury. Patients with impaired hepatic function tolerated topotecan doses of 1.5 mg/m$^2$ administered daily for 5 days without evidence of dose-limiting toxicity. For this reason, topotecan dose adjustments are not required for patients with liver dysfunction.

**Taxanes**

Taxanes are mainly metabolized by the liver, and undergo biliary excretion. A 96-hour infusion of paclitaxel was evaluated for patients with liver metastases and total bilirubin levels up to 2.0 mg/dL.\[14\] Metastatic liver disease was strongly correlated with reduced drug clearance, higher steady-state concentrations, and increased hematologic toxicity. A recommendation was made to dosereduce paclitaxel by 25% in patients with extensive liver metastases (extensive defined as masses greater than 2 cm or diffuse involvement).

A phase I trial of paclitaxel in 81 patients evaluated three cohorts with varying degrees of liver dysfunction.\[ 15\] The first cohort had AST elevations at least two times the ULN and bilirubin levels less than 1.5 mg/dL. The second cohort had bilirubin levels between 1.6 and 3.0 mg/dL with any AST level. The third cohort had bilirubin levels greater than 3.0 mg/dL with any AST level. Although the trial was initially designed to assess a 24-hour infusion schedule, it was extended to include a 3-hour regimen. Sixty patients were treated with the 24-hour infusion schedule and 21 patients with the 3-hour infusion schedule.

Patients in the first cohort were treated at a dose of 200 mg/m$^2$ over 24 hours. Five of seven patients experienced DLT, and it was clear that a dose de-escalation, rather than the planned dose escalation, would be necessary. The dose was decreased in subsequent groups of patients. Excessive DLT was experienced until the dose of 50 mg/m$^2$ was reached. None of the three patients treated at a dose of 50 mg/m$^2$ had a DLT. In the second cohort, the 24-hour infusion at a dose of 75 mg/m$^2$ caused DLT in two of six patients. In the third cohort, two of three patients had DLT at this dose and none of six at a dose of 50 mg/m2. For a 24-hour infusion of paclitaxel, doses greater than 50 to 75 mg/m$^2$ are not tolerated for patients with liver dysfunction. The most frequent DLT was myelosuppression, but neurotoxicity, mucositis, and asthenia were also seen.

The administration of paclitaxel over 3 hours in the setting of liver dysfunction is less clear. The study was closed prematurely due to the commercial availability of paclitaxel leading to poor accrual. Only one patient in the first cohort was treated with a 3-hour infusion, so no conclusion can be drawn for these patients with elevated AST and normal bilirubin. For patients in the second cohort, doses up to 100 mg/m$^2$ over 3 hours demonstrated safety with no DLTs. Two patients were treated at a dose of 125 mg/m$^2$, with one experiencing DLT, prior to study closure. Six patients in the third cohort were treated at a dose of 50 mg/m$^2$ with one DLT, and six patients were treated at a dose of 75 mg/m$^2$ with three patients experiencing DLTs. For moderate liver dysfunction (bilirubin: 1.6-3.0 mg/dL) 3-hour paclitaxel infusion can be given safely at a dose of 100 mg/m$^2$, while patients with severe liver dysfunction (bilirubin: > 3.0 mg/dL) will likely tolerate 50 mg/m$^2$. TABLE 1
Chemotherapeutic Agents for Which Dose Adjustment for Mild-to-Moderate Liver Dysfunction is Not Needed

**Table 1**

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<th>Agent</th>
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<tr>
<td>Capetaxel</td>
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<td>Cyclophosphamide</td>
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<td>Oxaliplatin</td>
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<td>Topotecan</td>
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Docetaxel (Taxotere) also requires dose adjustment for patients with liver impairment. Patients with liver impairment treated with docetaxel have demonstrated an increased risk of neutropenia and mucositis,[16] and treatment-related death.[17] There is a boxed warning in the docetaxel prescribing information stating that the drug should generally not be given to patients with bilirubin levels greater than the ULN, or to patients with AST and/or alanine aminotransferase (ALT) levels greater than 1.5 times the ULN concomitant with alkaline phosphatase levels greater than 2.5 times the ULN.[18]

Despite this, a case of successful docetaxel therapy in a woman with severe obstructive jaundice secondary to metastatic breast cancer has been reported.[19] The patient's pretreatment total bilirubin level was 12.0 mg/dL. Intravenous docetaxel was initiated at a dose of 20 mg/m²/wk. Due to myelosuppression after the first few cycles, the dosing schedule changed and docetaxel was administered whenever hematologic recovery (absolute neutrophil count [ANC] greater than 1,500 and platelet count greater than 75,000) occurred (range: 7-21 days). The patient had a sustained objective response to treatment. The major toxicity was a single episode of NCI-CTC grade 3 febrile neutropenia. While docetaxel may be used with caution in selected patients with hepatic dysfunction, further studies are required to determine the appropriate dose adjustments for patients with liver impairment.

**Platinum Agents**

The third-generation platinum oxaliplatin undergoes rapid biotransformation in the blood. It does not undergo cytochrome P450-mediated metabolism and is not associated with any hepatic enzyme- or protein-binding–based drug interactions. A phase I trial has been conducted in patients with normal, mild, moderate, and severe liver dysfunction (severe liver dysfunction was defined as a serum total bilirubin level greater than 3.0 mg/dL).[20]

Investigators found that oxaliplatin administered at the standard dose of 130 mg/m² every 21 days was well tolerated in patients with all levels of hepatic failure, and that liver dysfunction caused no apparent alteration in the clearance of platinum species from the plasma. There were no dose-limiting events at the maximum dose level tested. Unfortunately, they did not report the median or range for total bilirubin level in the severe liver dysfunction group. In addition, only three patients in the severe liver dysfunction group received the 130-mg/m² dose. Although it is likely that oxaliplatin is safe in patients with mild-to-moderate liver dysfunction, it remains unclear if full-dose oxaliplatin is safe in patients with markedly elevated serum bilirubin levels.

Cisplatin and carboplatin are primarily excreted by the kidney, and are therefore unlikely to require dose adjustments in patients with hepatic dysfunction. There are no formal studies evaluating the dosing of these agents in patients with liver failure. In a pilot study of 11 patients with liver dysfunction (bilirubin > 1.5 times the ULN) due to metastatic breast cancer, 10 patients showed improvement in liver function and 7 patients had a partial response after treatment with cisplatin and vinorelbine.[21] The patients received up to six cycles of cisplatin at a dose of 75 mg/m² every 21 days and vinorelbine at 20 mg/m² on days 1 and 8 of a 21-day cycle. One patient died from an
intracerebral hemorrhage that was possibly related to treatment. Myelosuppression was the most frequently reported adverse event. Other adverse events included nausea, vomiting, and mild neutropenia.

**Anthracyclines**

The anthracyclines are primarily metabolized and excreted by the liver. Doxorubicin is the anthracycline that has been studied most extensively in patients with poor liver function. The main toxicity of doxorubicin in the setting of liver dysfunction is myelosuppression. Other doxorubicin-induced toxicities are dependent on the peak concentration rather than the target drug concentration (area under the concentration-time curve [AUC]). Prolonged infusion schedules may reduce the risk of nonhematologic toxicity.[22,23]

In a study by Benjamin et al, severe toxicity (pancytopenia, mucositis, and three drug-related deaths) was documented in eight patients with hepatic impairment treated with full-dose doxorubicin.[24] An additional nine patients were treated with a dose-adjustment scheme based largely on the serum bilirubin concentration. Hematologic nadirs in these nine patients were similar to those of control patients, and no mucositis or drug-related deaths occurred. Based on these results, the investigators recommend (1) a 50% dose reduction of doxorubicin if the total bilirubin level is 2.0 to 3.0 mg/dL or if the serum transaminases are greater than three times the ULN, (2) a 75% dose reduction for total bilirubin levels between 3.0 and 5.0 mg/dL, and (3) withholding doxorubicin if the total bilirubin is greater than 5.0 mg/dL. In contrast, Donelli et al[3] contend that indiscriminate dose reductions are not warranted, and recommend dose adjustments only for serum total bilirubin greater than 3.0 mg/dL.

Unlike doxorubicin where dose adjustments are based on total bilirubin levels, epirubicin (Ellence) clearance has been shown to correlate with serum AST.[25,26] An elegant study by Dobbs et al evaluated an epirubicin dose-modification algorithm in breast cancer patients with liver impairment.[27] They identified the target plasma exposure to epirubicin that would be expected with standard dosing for patients with normal liver function. An epirubicin dosage scheme was designed, based on serum AST, that would achieve that target plasma level. A simple nomogram from which doses can be selected based on AST was devised and subsequently validated in 40 patients with liver dysfunction. Dobbs et al found that epirubicin dosing based on AST is safe and may reduce pharmacokinetic variability. These results are preliminary and further studies are warranted prior to the general acceptance of this nomogram.

**Vinca Alkaloids**

The biliary system is the main route of elimination of vincristine and vinblastine. For cholestatic patients, a small reduction in the vincristine dose resulted in a lower vincristine plasma AUC and less neurotoxicity.[28] It is recommended that vincristine and vinblastine be dose-reduced by 50% for patients with serum bilirubin levels between 1.5 and 3.0 mg/dL, and that they be withheld for levels greater than 3.0 mg/dL.[1] A pharmacokinetic study using a radioimmunoassay for vincristine demonstrated that patients with raised serum alkaline phosphatase levels, even when total bilirubin and transaminase levels are normal, have elevated AUC values.[29]

The vinorelbine package insert empirically recommends reducing the vinorelbine dose by 50% for serum bilirubin levels of 2.1 to 3.0 mg/dL and by 75% for bilirubin levels over 3 mg/dL.[30] In a pharmacokinetic study of 29 patients with advanced breast cancer (including 19 with liver metastases), a weak correlation between bilirubin and vinorelbine clearance was observed.[31] They found that vinorelbine clearance correlated significantly with the volume of liver replaced by tumor, and suggested reducing the dosage by 50% in all patients with diffuse liver metastases (defined as greater than 75% of liver volume replaced by tumor), regardless of serum bilirubin.

**Etoposide**

Etoposide circulates in the serum largely bound to albumin. The free fraction of drug is increased in the setting of hypoalbuminemia, resulting in a greater degree of hematologic toxicity.[32] It is excreted primarily in the bile. The decreased metabolic clearance in the setting of liver dysfunction can be compensated for by an increase in renal clearance. Patients with elevated bilirubin with preserved renal function and albumin levels may tolerate full doses of etoposide. Dose reduction is recommended for patients with hypoalbuminemia regardless of bilirubin level, or with renal insufficiency concomitant with liver dysfunction.
The general recommendation— that cyclophosphamide be administered at 75% of the standard dose for patients with serum bilirubin levels between 3.1 and 5.0 mg/dL and withheld in patients with serum bilirubin levels greater than 5.0 mg/dL—is not based on clinical trials.[1] Cyclophosphamide undergoes biotransformation to its active metabolite in the liver, which in turn gets inactivated, also in the liver. The overall exposure to the active metabolite does not change.

In a study of 17 patients with cirrhosis, 7 had severe hepatic dysfunction.[33] The half-life and clearance of cyclophosphamide in these patients differed significantly from those of patients with normal liver function, suggesting that cyclophosphamide accumulates in patients with liver disease. Since the metabolites of cyclophosphamide, not the parent compound, are responsible for both antitumor efficacy and toxicity, it is not surprising that few adverse effects were demonstrated in the setting of liver dysfunction. It is not known if clinical efficacy is altered in patients with impaired hepatic function due to decreased activation of the drug.

Mechlorethamine

Mechlorethamine (Mustargen) undergoes rapid chemical transformation and combines with water or reactive compounds of cells so that the drug is no longer present in active form a few minutes after administration. In a retrospective study of patients with advanced lymphoma and severe liver dysfunction (mean total bilirubin of 10.7 mg/dL and median alkaline phosphatase of 982 U/L), mechlorethamine was given at a dose of 6 mg/m²/wk in combination with corticosteroids with or
without rituximab (Rituxan).[34] Approximately 80% of the patients had a poor performance status prior to the start of therapy. With treatment, 54% of patients had sufficient improvement in liver function to receive subsequent therapy, most often with CHOP (cyclophosphamide, doxorubicin HCl, vincristine [Oncovin], prednisone), and 22% of patients were alive and disease-free at a median follow up of 31 months. The median level of bilirubin at the time of subsequent CHOP therapy was 2.1 mg/dL (range: 0.8-8.3 mg/dL). The authors recommend that patients with lymphoma and severe liver dysfunction receive concomitant mechlorethamine, highdose methylprednisolone, and rituximab as indicated. This combination may be used as a bridge to conventional regimens.

Conclusions

Although many patients receiving cytotoxic chemotherapy have abnormal liver function test values, there is no accepted system to define liver dysfunction in patients with cancer. The serum bilirubin level is the most frequently utilized parameter to adjust chemotherapy dosing, but for certain drugs, transaminase levels, serum alkaline phosphatase levels, and/or serum albumin levels have been shown to play an important role. The question remains as to whether patients with tumor-related organ dysfunction should be approached differently than those with baseline (non-tumor-related) organ dysfunction. It would seem logical to take a more aggressive antineoplastic treatment approach in patients whose liver impairment is secondary to tumor infiltration. Nevertheless, caution in treating all patients with hepatic failure is essential.

TABLE 2

Recommended Dose Adjustment for Liver Dysfunction

For the majority of chemotherapeutic agents, there is a paucity of data to guide dosing in the setting of liver impairment—especially severe liver impairment (serum bilirubin: > 5 mg/dL). From the available data, it appears that continuous-infusion 5-FU, capecitabine, gemcitabine, mechlorethamine, cyclophosphamide, topotecan, and oxaliplatin are relatively safe, at least for patients with mild-to-moderate liver dysfunction (see Table 1). On the contrary, taxanes, vinca alkaloids, irinotecan, and anthracyclines may result in unacceptable toxicity (see Table 2 for recommended dose adjustments). There are very few data regarding combination regimens. Likewise, there are few data regarding the antitumor efficacy of chemotherapy in this setting. Further well-designed studies are undoubtedly needed.

Financial Disclosure: The authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

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