Part II: Liver function in oncology: towards safer chemotherapy use

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The liver is fundamentally important in drug metabolism. In oncology, the astute clinician must not only understand the meaning and limitations of commonly ordered liver biochemical tests, but also be aware of which anticancer agents might induce liver dysfunction, and of the strategies for appropriate dosing of patients with pre-existing liver dysfunction. In part I of our Review, we highlighted both the importance and inadequacies of identifying serum biochemical liver abnormalities in oncology; we also discussed a lack of routine formal investigation of liver function. We summarised chemotherapy-related hepatotoxicity and other causes of liver toxic effects in patients with cancer. Here in part II, we discuss trials that have specifically assessed chemotherapy dosing strategies in the setting of overt biochemical liver dysfunction and we note their recommendations. Furthermore, we review other assessments of liver metabolic and excretory function, particularly in the setting of chemotherapy drug handling. We discuss the potential use of these metabolic probes in practice.

Introduction
Primum non nocere—to first, do no harm—is a fundamental law of medicine learnt by all clinicians. In oncology, chemotherapy is given to patients with the inherent premise of an anticancer effect; however, some of the most toxic medications in clinical practice are used, and there can be a narrow margin between benefit and risk. Their therapeutic index is made even narrower by the presence of pre-existing organ impairment such as liver or kidney dysfunction, which can increase the risk of drug toxic effects. Alternatively, liver impairment could reduce the activation of prodrugs, reducing the chance of a meaningful response. Liver injury and the resulting biochemical abnormalities are common in patients with cancer, and can be due to metastases (figure 1), concomitant drugs, or past liver damage such as cirrhosis (figure 2). The choice of anticancer agent and its dose must be considered carefully to meet the pledge made to patients—to do more good than harm.

Underlying liver dysfunction and anticancer agents
Many chemotherapy agents are substrates for liver uptake, metabolism, and excretion, and dysfunction of the liver can result in drug toxic effects (or reduced activation of prodrugs). Is the effect substantial? Pre-existing liver impairment (other than in Child’s class C cirrhosis) is thought to have only modest effects on the elimination and toxic effects of drugs. Nevertheless, a typical patient presents with several variable causes of liver impairment, including direct hepatic involvement by their disease, effects of cancer-induced inflammatory cytokines, comorbidities, and concurrent medications (both prescription and complementary).

Patients with aberrant chemotherapy drug metabolism have substantial risk of severe haematological and non-haematological toxic effects: caution must be exercised with specific chemotherapy drugs. However, substantial dose reductions might reduce therapeutic effectiveness.

Many phase I, phase II, and phase III clinical trials have excluded patients with abnormal liver function (ie, with abnormal serum liver biochemical tests). Therefore, less is known about the most appropriate starting doses of chemotherapy in these individuals. Anticipated toxic effects based on trials cannot necessarily be extrapolated to this group of patients, and commonly dose reductions are empirical and not evidence-based.

Over the past decade, several trials have assessed chemotherapy drug pharmacokinetics specifically in patients with liver dysfunction. The trials have aimed to develop specific dosing guidelines on the basis of standard biochemical tests of liver function. Patients have been entered into distinct dose cohorts defined by a combination of standard serum liver biochemistry results. Dose can be escalated if there is no evidence of dose-limiting toxic effects. Of note, the numbers in the cohorts are small,
and these trials are only a small evidence base for use of these agents in liver dysfunction. Table 1 summarises the main drugs for which pharmacokinetic studies have been done in the setting of liver dysfunction, and shows dose recommendations from the trial researchers on the basis of available evidence. Some of the more commonly used drugs that have been assessed in this setting are discussed below.

Paclitaxel
A member of the taxane family, paclitaxel is mainly metabolised by the liver through the cytochrome 2C8 and 3A4 pathways; it undergoes biliary excretion through the action of ABCB1 (ATP binding cassette subfamily B member 1).

A prospective study of toxic effects and pharmacokinetics in 81 patients grouped into three cohorts according to liver dysfunction showed that patients with abnormal bilirubin (ie, >25 μmol/L) or aspartate aminotransferase levels 2-times or higher than the upper limit of normal had more toxic effects (particularly myelo suppression) compared with other groups and warranted routine dose-reduction. Compared with historical controls, those who received a 3-h paclitaxel infusion (the most common method of administration) had protracted plasma paclitaxel concentrations that exceeded 0.05 μmol/L—the pharmacokinetic measure associated with reduction in neutrophils.

Docetaxel
Also a taxane, docetaxel undergoes hydroxylation by cytochrome P450 3A4 and is mainly faecally excreted. A prospective study assessed the association between serum liver biochemistry, cytochrome P450 3A4 activity (via the erythromycin breath test), and docetaxel clearance in patients with cancer. Patients were divided into cohorts on the basis of baseline serum liver biochemistry, ranging from normal to severely abnormal, and received different initial docetaxel doses. Drug clearance was lower in patients with moderate to severely abnormal liver tests than in those with normal to mildly abnormal tests. Five of eight patients with normal liver tests but with cytochrome P450 3A4 activity lower than the norm had reduced docetaxel clearance. The researchers concluded that liver biochemical tests alone do not explain variability in docetaxel clearance.

Gemcitabine
A pyrimidine analogue, gemcitabine is metabolised intracellularly by nucleoside kinases, and mainly excreted in urine. In one study, gemcitabine was analysed in a cohort of 40 patients with liver impairment. Patients with elevated aspartate aminotransferase (ie, ≥2-times the upper limit of normal) did not have increased toxic effects with gemcitabine. However, patients with elevated bilirubin levels (ie, >27 μmol/L) had substantial liver dysfunction induced by gemcitabine and dose reductions were recommended. There were no apparent pharmacokinetic differences between groups.

Irinotecan
A topoisomerase I inhibitor prodrug that is metabolised to the active SN38 by carboxyl esterase, irinotecan excretion is mainly biliary after inactivation from glucuronide conjugation by hepatic uridine diphosphate glucuronosyltransferase-1A1 (UGT1A1) to generate SN38G. Irinotecan is also inactivated through oxidation of its bipiperidine
sidechain by cytochrome P450 3A4, generating the inactive APC (7-ethyl-10-[4-N-5-aminopentanoic-acid]-1-piperidino] carbonyloxycamptothecin) and NPC (7-ethyl-10-[4-amino-1-piperidino] carbonyloxycamptothecin).

Two phase 1 studies assessed the pharmacokinetics of irinotecan given every 3 weeks in patients with varying degrees of liver dysfunction. Raymond and colleagues grouped patients according to serum bilirubin levels. Elevated bilirubin (ie, >1·5-times upper limit of normal) was associated with irinotecan toxic effects (grade 4 febrile neutropenia and diarrhoea). Increased bilirubin and alkaline phosphatase were associated with decreased irinotecan clearance (and that of its metabolites SN38, SN38G, and APC). The authors concluded that decreased clearance was related to decreased biliary excretion.

<table>
<thead>
<tr>
<th>Anticancer agent</th>
<th>Effect of liver impairment</th>
<th>Dose modification</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalosporin</td>
<td>Increased aspartate aminotransferase or bilirubin: no relation to pharmacokinetics or toxic effects</td>
<td>No dose adjustment needed</td>
<td>2</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>No changes in clearance</td>
<td>No dose adjustments needed</td>
<td>4</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Increased risk of neutropenia, mucositis, and death</td>
<td>Use not recommended if bilirubin is more than upper limit of normal, or if ratio of aspartate aminotransferase to alanine aminotransferase is &gt;1·5-times upper limit of normal and alanine phosphatase is &gt;2·5-times upper limit of normal</td>
<td>5, 6</td>
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<tr>
<td>Doxorubicin</td>
<td>Myelosuppression, mucositis</td>
<td>Bilirubin &lt;51 μmol/L: normal dose</td>
<td>4</td>
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<td></td>
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<td>Bilirubin 34–51 μmol/L: decrease dose by 50%</td>
<td>7</td>
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<tr>
<td></td>
<td></td>
<td>Bilirubin 51–85 μmol/L: decrease dose by 75%</td>
<td>7</td>
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<tr>
<td></td>
<td></td>
<td>Bilirubin &gt;85 μmol/L: withhold treatment</td>
<td>7</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>Aspartate aminotransferase more sensitive marker of clearance than bilirubin</td>
<td>Consult dose guidelines based on levels of aspartate aminotransferase</td>
<td>8</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>Increased aspartate aminotransferase or bilirubin</td>
<td>Aspartate aminotransferase ≥3-times upper limit of normal or bilirubin 17–120 μmol/L: 50% dose reduction</td>
<td>9</td>
</tr>
<tr>
<td>Etoposide</td>
<td>Mild to moderate impairment: no pharmacokinetic effect</td>
<td>Unclear (increased renal clearance might compensate)</td>
<td>10</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>Increased bilirubin: no relation to toxic effects</td>
<td>No dose adjustment needed</td>
<td>11</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Increased aspartate aminotransferase alone: no increase in toxic effects</td>
<td>Usual dose: 1000 mg/m²</td>
<td>12</td>
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<tr>
<td></td>
<td>Increased bilirubin: deterioration in liver function</td>
<td>Increased aspartate aminotransferase: no dose change needed</td>
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<td></td>
<td></td>
<td>Increased bilirubin: reduce dose by 20% (ie, to 800mg/m²) and increase if tolerated</td>
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<tr>
<td>Imatinib</td>
<td>No notable pharmacokinetic differences or increased toxic effects</td>
<td>Stop treatment if hepatotoxicity develops, should probably not rechallenge</td>
<td>13</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>Increased aspartate aminotransferase alone: no increase in toxic effects</td>
<td>Increased aspartate aminotransferase: no dose change</td>
<td>14–16</td>
</tr>
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<td></td>
<td>Increased bilirubin: neutropenia and diarrhoea</td>
<td>Increased irinotecan: reduce dose: 3-weekly irinotecan (usual dose 350 mg/m² every 3 weeks)</td>
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<td></td>
<td></td>
<td>• Bilirubin &lt;1·5-times upper limit of normal: 350 mg/m²</td>
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<td>• Bilirubin &gt;1·5-3-times upper limit of normal: 200 mg/m²</td>
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<td>• Bilirubin &gt;3-times upper limit of normal: irinotecan not recommended</td>
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<td></td>
<td>Weekly irinotecan (usual dose 125 mg/m² for 4 of 6 weeks)</td>
<td>Weekly irinotecan (usual dose 125 mg/m² for 4 of 6 weeks)</td>
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<td>• Bilirubin 1·5–3-times upper limit of normal and ratio of aspartate aminotransferase to alanine aminotransferase &lt;5-times upper limit of normal: 60 mg/m²</td>
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<td>• Bilirubin 1·5–3-times upper limit of normal and ratio of aspartate aminotransferase to alanine aminotransferase &lt;5-times upper limit of normal: 100 mg/m²</td>
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<td>• Bilirubin &gt;3-times upper limit of normal: irinotecan not recommended</td>
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<td>• Bilirubin 1·5–3-times upper limit of normal and ratio of aspartate aminotransferase to alanine aminotransferase &lt;5-times upper limit of normal: 100 mg/m²</td>
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<td>• Bilirubin &gt;3-times upper limit of normal and ratio of aspartate aminotransferase to alanine aminotransferase &lt;5-times upper limit of normal: 200 mg/m²</td>
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<td>• Bilirubin &gt;3-times upper limit of normal and ratio of aspartate aminotransferase to alanine aminotransferase: reduce dose by 20% (ie, to 800mg/m²) and increase if tolerated</td>
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<tr>
<td>Paclitaxel</td>
<td>Increased aspartate aminotransferase or bilirubin increases myelosuppression</td>
<td>No dose adjustment</td>
<td>17</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Increased aspartate aminotransferase or bilirubin increases myelosuppression</td>
<td>Reduce dose if increased aspartate aminotransferase or increased bilirubin</td>
<td>18</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Clearance does not differ between patient cohorts</td>
<td>Bilirubin ≤1·5-times upper limit of normal: 400 mg twice a day</td>
<td>19</td>
</tr>
<tr>
<td>Sorafenib</td>
<td></td>
<td>Bilirubin 1·5–3-times upper limit of normal: 200 mg twice a day</td>
<td></td>
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<tr>
<td>Sorafenib</td>
<td></td>
<td>Bilirubin 3–10-times upper limit of normal: sorafenib not recommended</td>
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<tr>
<td>Sorafenib</td>
<td></td>
<td>Albunin &lt;25 g/L: 200 mg daily</td>
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<tr>
<td>Topotecan</td>
<td>No obvious effects</td>
<td>No dose adjustment needed if bilirubin 29–84 μmol/L</td>
<td>20</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>Increased bilirubin decreases drug clearance</td>
<td>Suggested dose:</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Volume of liver affected correlates with clearance</td>
<td>Bilirubin 2·1–3-times upper limit of normal: reduce dose by 50%</td>
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<td></td>
<td></td>
<td>Bilirubin &gt;3-times upper limit of normal: reduce dose by 75%</td>
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<td></td>
<td></td>
<td>Diffuse liver metastases: decrease dose by 50% (irrespective of bilirubin concentration)</td>
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Table 1: Anticancer agents specifically studied in setting of liver dysfunction
Venook and colleagues found that those with increased aspartate aminotransferase (i.e., ≥3-times upper limit of normal) but normal bilirubin did not have toxic effects or changes in drug clearance. However, those with increased bilirubin (i.e., 17.1–120 μmol/L) had dose-limiting toxic effects, with decreased irinotecan and SN38 clearance.

Schaaf and colleagues assessed irinotecan pharmacokinetics in patients who were prospectively classified into four groups on the basis of baseline serum bilirubin, alanine aminotransferase, and aspartate aminotransferase, and who were given low-dose weekly irinotecan ranging from 40 mg/m² to 75 mg/m². Compared with controls, all groups had reduced irinotecan clearance (by 30–70%) and an increased dose-adjusted SN38 area under the curve (AUC, 33–216%). There was a strong linear correlation between irinotecan AUC or SN38 AUC and serum bilirubin, which plateaued with increasing aspartate aminotransferase. These studies and others show that irinotecan clearance correlates with serum bilirubin more than with other biochemical markers of liver function.

**Erlotinib**

An oral epidermal growth factor receptor-1 associated tyrosine kinase inhibitor for use in non-small-cell lung cancer, erlotinib is mainly metabolised by liver cytochrome P450 3A4 and to a lesser degree by cytochrome P450 1A2.

A phase I study analysed this drug’s pharmacokinetics in patients with liver or kidney dysfunction. The study showed a longer half-life, reduced clearance, and increased likelihood of dose-limiting toxic effects (particularly with a bilirubin rise to ≥1.5-times baseline) in the 36 patients with liver dysfunction (defined as aspartate aminotransferase ≥3-times upper limit of normal, with or without albumin <25 g/L). This study recommended a 50% dose reduction in patients with this level of liver dysfunction. A pharmacokinetic analysis of more than 1000 patients who received erlotinib found that total bilirubin, in addition to α-1 acid glycoprotein and smoking status, were the most important factors that affected drug clearance.

**Fluorouracil**

This drug is eliminated by liver and peripheral metabolism through dihydropyrimidine dehydrogenase. Fluorouracil has been assessed in 64 patients with solid tumours who had liver dysfunction (i.e., bilirubin 25–85 μmol/L or >85 μmol/L) in a phase I setting. Patients received a 24-h infusion of fluorouracil and leucovorin on a weekly regimen. The study recorded no relation between bilirubin and fluorouracil clearance or toxic effects. This finding suggests that infused fluorouracil is fairly safe to use in patients with liver dysfunction, although regular monitoring with liver tests is advised.

However, there have been reports of substantial toxic effects when fluorouracil has been given to patients with serum bilirubin levels higher than 85 μmol/L, and case reports exist of this drug potentially contributing to liver dysfunction.

**Sorafenib**

An orally available multi-kinase inhibitor, sorafenib is effective against renal-cell carcinoma and hepatocellular carcinoma. It is mainly metabolised in the liver through both an oxidative pathway mediated by cytochrome P450 3A4 and also UGT1A9-mediated glucuronidation; most is faecally excreted.

A phase I study of sorafenib in patients with liver dysfunction who were divided into groups on the basis of bilirubin levels, albumin levels, and renal function found that although drug clearance did not differ between groups, dose-limiting toxic effects occurred with increasing bilirubin levels and decreased albumin (i.e., <25 g/L).

**Other methods to estimate liver function**

It would be best to establish an individualised chemotherapy dosing nomogram on the basis of patient phenotypic or genomic metabolic, excretory, and pharmacodynamic differences. The current method of chemotherapy dose determination on the basis of body surface area does not take into consideration variability between patients and has poor correlation to drug clearance.

Alternative, but feasible, methods for safe and effective chemotherapy dosing are needed. Table 1 shows trials and their recommended routine dose reductions in patients with overt biochemical liver dysfunction; however, they do not predict dose adjustments that might be needed because of individual variability in liver-disposition pathways that are not functionally tested by serum biochemistry. Given such limitations, several dosing strategies have been assessed, many of which have been reported in the general pharmacology literature and are used in critical care, liver transplantation, or assessment of residual liver function when planning liver resection. Data are emerging for these tests in the setting of chemotherapy administration.

Many alternative tests are in vivo or indirect probes of hepatic cytochrome P450 activity. Of note, different probes for the same enzyme do not always correspond to each other, given differences in substrate avidity. Moreover, other factors are involved in drug metabolism or excretion, including regulation and activity of other Phase I enzyme reactions (e.g., oxidation/reduction and hydrolysis) and Phase II metabolic reactions (e.g., glucuronidation, sulphation, or glutathione conjugation), and biliary excretion through ABC (ATP-binding cassette) membrane pumps (e.g., ABCB1, ABCC1, ABCC2, and ABCG2).

The applicability of such probes to clinical practice has been questioned. However, to date they relate to pharmacokinetics for many antinecancer agents, and many believe they will continue to be used in research, drug development, and eventually in routine clinical practice. These probes are outlined in table 2.
Breath tests

The Carbon-14 N-methyl-erythromycin breath test is an in vivo probe of liver enzyme function. It is a quantitative measure of hepatic cytochrome P450 3A4 activity, and measures phenotypic variance in enzyme activity due to genetic polymorphisms, disease factors, or concomitant drugs.

Erythromycin is a substrate for cytochrome P450 3A4, but it is also transported by ABCB1. Hepatic cytochrome P450 3A4 demethylates intravenous ¹⁴C-(N-methyl)-erythromycin to generate ¹⁴CO₂. The test is done by intravenous administration of trace ¹⁴C-erythromycin and measurement of amount of exhaled ¹⁴CO₂. It has been the most widely assessed probe in oncology.

A study of 134 patients with cancer analysed factors that affect cytochrome P450 3A4 activity by use of the erythromycin breath test. Enzyme activity varied by up to 14-times in patients. In a multivariate analysis, enzyme activity was not significantly affected by patient demographics, but liver function combined with the concentration of the acute-phase reactant α-1 acid glycoprotein accounted for about 18% of overall variation in cytochrome activity (p<0.001). The researchers concluded that baseline demographic, physiological, and genetic polymorphisms have a minor effect on phenotypic cytochrome P450 3A activity in patients with cancer.

Docetaxel

Docetaxel is one of the most commonly studied anticancer agents for these probes. Erythromycin breath-testing has been extensively investigated for optimisation of docetaxel dosing.

One study measured baseline hepatic cytochrome P450 3A4 activity by use of the erythromycin breath test in 21 patients who subsequently received docetaxel every 3 weeks. The breath-test measurement (proportion of ¹⁴CO₂ exhaled in 1 h) was the best predictor of docetaxel clearance compared with serum liver biochemistry and α-1 acid glycoprotein, accounting for 67% of variability between patients. Two patients with the lowest breath-test measurement had the lowest docetaxel clearance and the most severe toxic effects.

A model based on this breath-test measurement and serum albumin has been assessed for tailored docetaxel dosing in 28 patients with advanced breast cancer. Baker and colleagues found that erythromycin breath-testing
was a more accurate predictor of docetaxel clearance than was serum biochemical testing of liver function. The association between the breath-testing and docetaxel clearance was confirmed with a weekly docetaxel regimen.38 Erythromycin breath-testing could eventually lead to more selective use of docetaxel in practice. However, this test is not associated with vinorelbine clearance.39

Fluorouracil
Toxic effects with this drug might be related to deficiency or reduced activity of dihydropyridine dehydrogenase, which mediates catabolism of up to 80–90% of the drug to 5-fluorodihydouracil and after several other steps to ammonia and CO₂. Up to 5% of the general population have complete or partial deficiency of dihydrofolate dehydrogenase,39 and its deficiency in patients with cancer is associated with severely reduced fluorouracil clearance and increased toxic effects (some fatal).

However, not all patients who present with severe fluorouracil-induced toxic effects are dihydrofolate-dehydrogenase deficient. The 2-¹³C-uracil breath test is a phenotypic screen for dihydrofolate-dehydrogenase deficiency in patients who receive fluorouracil and has 96% specificity and 100% sensitivity. Furthermore, in one study, a 2-¹³C-fluorouracil breath test for assessment of dihydrofolate-dehydrogenase activity identified patients with severe and moderate toxic effects.

Drug-clearance tests
Midazolam clearance
An alternative method of assessment of hepatic cytochrome P450 3A activity, midazolam is almost entirely metabolised by this enzyme family and is not an ABCB1 substrate. It has been analysed in patients with cancer receiving docetaxel. A study of 56 patients with advanced cancer with normal liver function found that high midazolam concentration or low clearance (indicating low cytochrome activity) was associated with severe neutropenia and febrile neutropenia.

Another study of 30 patients compared the midazolam-clearance test with the erythromycin breath test for assessment of irinotecan clearance. Cytochrome P450 3A4 activity varied by seven-times between patients on erythromycin breath-testing, but was not associated with irinotecan clearance. Midazolam clearance varied four-times, but was strongly associated with irinotecan clearance. This parallel could arise because erythromycin is rapidly metabolised by cytochrome P450 3A4, and ABCB1 might play a part in its disposition compared with irinotecan.

Plasma and urinary steroid clearance
As an in-vivo probe of cytochrome P450 3A metabolism, specifically in patients with cancer, this method has been studied as a predictor of vinorelbine clearance in 20 patients. Measurement of dexamethasone plasma clearance and alkaline phosphatase in a covariate model significantly decreased variability between individuals in vinorelbine clearance, by contrast with dosing based on body surface area. Dexamethasone as a probe for cytochrome P450 3A4 predicted docetaxel clearance in females, but not males.35

Steroid metabolite excretion in urine has been used as a surrogate of cytochrome P450 3A4 activity. 24-h urinary 6-β-hydroxycortisol level after cortisol administration is significantly associated with docetaxel clearance. Of 50 patients who were randomly assigned a docetaxel dose based on body surface area or an individualised dose based on clearance estimated from the probe, the latter was able to decrease the pharmacokinetic variability of docetaxel.36

Indocyanine green plasma disappearance rate
Indocyanine green is a water-soluble dye given intravenously, which is almost completely eliminated unchanged into bile without enterohepatic circulation. Elimination is dependent on hepatic blood flow, cellular uptake, and excretion. As a marker of liver perfusion and function, it is a good predictor of survival in critically ill patients. This dye is thought to be more sensitive than serum bilirubin or enzyme tests for assessment of liver dysfunction and prediction of prognosis, and has been used to assess liver functional reserve before resection.

The probe has been assessed in the setting of irinotecan use, where AUC significantly correlates with indocyanine green plasma disappearance rate; AUC of SN38, its active metabolite, also correlates with disappearance rate. However, to our knowledge there have been no published investigations of the efficacy of this test for prediction of toxic effects from, or pharmacokinetics of, other anticancer agents.

Antipyrine clearance test
Antipyrine is an analgesic that is metabolised by several cytochrome P450 enzymes (1A2, 2B6, 2C, and 3A4), and is widely used as a measure of overall liver oxidative capacity. Antipyrine has proved useful for assessment of liver metabolic function in various liver diseases—before and after transplantation and for assessment of drug interactions.

The test is simple and relatively inexpensive. In patients with cancer, Gurney and colleagues found that the antipyrine-clearance test correlated with epirubicin AUC and clearance, and with drug-induced neutropenia. Activated partial thromboplastin time, international normalised ratio, and serum bilirubin correlated with some epirubicin pharmacokinetics, but aminotransferase levels did not. Importantly, body surface area was not associated with pharmacokinetic parameters or degree of neutropenia. A relation between antipyrine clearance and neutrophil nadir has also been shown in patients who received docetaxel and cisplatin in combination.

Liver functional imaging
Liver functional imaging aims to provide a non-invasive method of assessing drug uptake and excretion by the liver.
This imaging uses radiotracers that have the same liver cellular transport carriers as those for a particular cytotoxicity.

Biliary transporter-mediated excretion has an important role in drug clearance by the liver; several enzymes are involved including ABCB1, ABCC1, ABCC2, and ABCG2. Their substrates include vinca alkaloids, anthracyclines, taxanes, and irinotecan. Variable activity of these enzymes could contribute to variation between patients in drug clearance from the liver and systemic circulation.

Functional imaging by use of technetium-99-sestamibi ([⁹⁹mTc]MIBI), an ABCB1 substrate (and to a lesser extent ABCC1 and ABCC2) has been assessed in patients with cancer. Comparisons of liver [⁹⁹mTc]MIBI elimination rate with ABCB1 genotype in 66 patients found 12-times variation in the elimination constant for [⁹⁹mTc]MIBI, which did not correlate with test results of serum biochemical liver function. There was a significant association between some common single nucleotide polymorphisms in ABCB1 and elimination constant. This nuclear imaging could be a pretreatment indicator of drug clearance.

[⁹⁹mTc]MIBI liver imaging has been assessed with vinorelbine treatment in a study of 41 patients. The study used the midazolam-clearance test (to assess cytochrome P450 3A phenotype), [⁹⁹mTc]MIBI (to assess ABCB1 phenotype), and genotype testing for both enzymes to predict vinorelbine clearance and frequency of myelosuppression. [⁹⁹mTc]MIBI clearance (a product of liver volume and MIBI elimination rate constant) was an independent predictor of vinorelbine clearance, which significantly correlated with fractional survival of neutrophils. Midazolam clearance did not correlate with vinorelbine pharmacokinetics or toxic effects. An alternative method of vinorelbine dosing could be a fixed dose guided by these pre-treatment investigations of liver function.

The oral tyrosine kinase inhibitor imatinib is mainly metabolised by liver cytochrome P450 3A enzymes and eliminated unchanged in bile, presumably via ABCB1 and interaction with ABCG2. Several researchers have assessed the pharmacogenetics of enzymes in imatinib metabolism, but genetic testing can be expensive. Therefore, alternative probes for phenotypic differences in enzyme activity are under investigation. 22 patients treated with imatinib were assessed for pharmacokinetic data by use of erythromycin breath-testing, midazolam clearance, and genotyping for single nucleotide polymorphisms in CYP3A and ABCB1. Erythromycin breath-testing and midazolam clearance were associated with imatinib clearance, but [⁹⁹mTc]MIBI liver clearance was not. However, a reduction in [⁹⁹mTc]MIBI liver clearance was seen in patients with some ABCB1 genotypes, suggesting that this test might benefit some individuals.

Two types of liver nuclear imaging have been assessed in relation to irinotecan pharmacokinetics: [⁹⁹mTc]DIDA (acetanilidoiminodiacetic acid) or [⁹⁹mTc]DISIDA (disofenin)—both of which are substrates for ABCC1 and ABCC2—and [⁹⁹mTc]MIBI. These substrates are excreted by the same biliary transporters involved in excretion of irinotecan and its active metabolite SN38. An exploratory study in 21 patients with colorectal cancer who received irinotecan used [⁹⁹mTc]MIBI, iminodiacetic acid analogue-imaging, and relevant genotyping to identify correlates with drug pharmacokinetics. For both nuclear probes, the proportion retained at 1 h correlated linearly with SN38 AUC, suggesting that reduced tracer clearance could be associated with increased SN38 exposure which could be a predictor of irinotecan toxic effects. Increasing grade of neutropenia was associated with reduced iminodiacetic acid hepatic-extraction fraction (a measure of drug uptake by the liver), but not significantly so. Increased liver uptake and rapid clearance of MIBI was associated with severity of diarrhoea. However, this study analysed few patients and further investigation of the efficacy of functional imaging is warranted.

Scoring systems for severe liver disease
Gastroenterologists and hepatologists commonly assign a score to patients with chronic liver disease, on the basis of validated systems, to estimate outlook in terms of disease burden and ability to withstand the stress of major surgery. These systems generally use a combination of biochemical and clinical assessments, but are used less often in oncology. Nevertheless, awareness of alternative methods of assessing liver functional impairment can be useful. If remaining liver capacity might necessitate transplantation, then chemotherapy should probably not be given. In patients with cancer other than hepatocellular carcinoma, transplantation is rare because malignant disease is almost always a contraindication.

Child-Turcotte-Pugh score
This score is a combined measure based on extent of clinical ascites, encephalopathy, and laboratory indices including albumin, international normalised ratio, and bilirubin. It was originally developed to assess the ability of patients with cirrhosis from alcohol use (figure 2) and oesophageal varices to withstand portacaval shunt surgery to reduce the risk of bleeding. However, except for hepatocellular carcinoma, the Child-Turcotte-Pugh score is not generally used in oncology to determine chemotherapy dosing. A phase I study assessed erlotinib in liver or kidney dysfunction and found no relation between score and erlotinib clearance, although increased aspartate aminotransferase or bilirubin predicted drug toxic effects.

Model for end-stage liver disease (MELD)
This scoring system was developed in 2000 and has been used since 2002 to prioritise patients for liver transplantation by use of a mathematical equation that incorporates bilirubin, international normalised ratio, and serum creatinine. In oncology, the model for end-stage transplantation is rare because malignant disease is almost always a contraindication.
liver disease has mainly been used to prioritise patients with hepatocellular carcinoma for transplantation; in the USA it has led to an increase in the proportion of transplants due to hepatocellular carcinoma.\textsuperscript{49} Survival after transarterial chemoembolisation for hepatocellular carcinoma is associated more closely with Child-Turcotte-Pugh score than with the score from the model for end-stage liver disease.\textsuperscript{70}

**Pharmacogenomics**

Pharmacogenomics has been studied with much interest with regard to chemotherapy drugs and has expanded in recent years because of increased knowledge from studies such as the Human Genome Project. Tests can detect single nucleotide polymorphisms and deficiencies in enzymes that are commonly involved with liver metabolism (eg, cytochrome P450 and UGT1A1) and excretion (eg, ABCB1). Many studies have shown associations between particular genotypes and drug clearance or metabolism. Genetic factors that are thought to contribute to drug toxic effects include dihydropyridine-dehydrogenase deficiency resulting in toxic effects from fluorouracil, and UGT1A1 deficiency resulting in irinotecan toxic effects.

Genetic heterogeneity means that although quantitative enzyme deficiency might not be present, polymorphisms can lead to variable clearance in individuals as identified by genetic or phenotypic tests. Drug effectiveness and toxic effects might be predicted by genotyping of pharmacodynamic pathways.\textsuperscript{71,72} However, it would be simplistic to assume that all variation in drug handling or effect can be described by the characterisation of one metabolic or excretory pathway, and the following need consideration: other pathways; differences in host and tumoral drug sensitivity; the paraneoplastic effects of the tumour on host metabolic phenotype; and variation in populations or between ethnic groups.

Not all pharmacogenomic studies have shown significant associations with drug pharmacokinetics. Fluorouracil dosing on the basis of genotyping its main metabolic enzyme (dihydropyridine dehydrogenase) is one example. Activity of this enzyme and the presence of a common splice-site mutation in patients with severe fluorouracil-induced grade 3–4 toxic effects\textsuperscript{48} showed only 60% had decreased enzyme activity in peripheral-blood mononuclear cells, 42% of which were heterozygous for the variant and one patient homozygous. The splice-site mutation was also present in 4% of patients with normal dihydropyridine-dehydrogenase activity.\textsuperscript{73} Therefore, deficiency of this enzyme is not solely due to inactivating mutations.\textsuperscript{71,72,73}

Moreover, toxic effects from fluorouracil occur in patients with normal dihydropyridine-dehydrogenase activity, suggesting that other genes of pyrimidine catabolism might have a role.

Variability between individuals in paclitaxel pharmacokinetics was not explained by alleles for CYP2C8, CYP3A4, CYP3A5, and ABCB1 from DNA analyses of 97 patients.\textsuperscript{73} A study of 25 patients that assessed vinorelbine pharmacokinetics found no relation between cytochrome P450 3A5 activity or erythromycin breath-testing and vinorelbine clearance or toxic effects.\textsuperscript{71}

Therefore, current pharmacogenomic analyses might aid only the dosing for some anticancer agents and possibly selected patients. For example, alleles in ABCB1 are associated with docetaxel-induced neuropathy, grade of neutropenia, and overall survival in patients with prostate cancer.\textsuperscript{71}

The ideal use of such tests would be to reduce the frequency and severity of adverse drug reactions. Genetic variation is thought to cause more than 50% of these reactions.\textsuperscript{71} Although costs might prevent genetic testing, money could be saved from treatment of adverse effects, and so too could lives, by further development of alternative methods of assessing liver function and predicting appropriate dose on an individual basis.

**Conclusion**

The past decade has seen increased recognition of the limitations of current biochemical tests of liver function to predict hepatotoxicity and other systemic toxic effects from chemotherapy. Furthermore, understanding and characterisation of genetic polymorphisms has been enhanced; these can be analysed genotypically and phenotypically to accurately characterise and predict effectiveness and toxic effects of anticancer agents.

Given these encouraging findings, why is there not a stronger push to use these newer, more effective tests of liver function and drug metabolism more rapidly and commonly in oncology? First, more research in larger populations is needed to show safe and effective chemotherapy dosing on the basis of adjustments for liver synthetic and enzyme function with the new tests. Population models must be validated, which incorporate all factors that are known to affect frequency of toxic effects (including genotyping and phenotyping of pharmacodynamic pathways, extent and type of past treatment, and other individual characteristics). Second, randomised phase III trials are needed to show that dosing by genotype–phenotype nomograms reduces the risk of drug toxic effects while maintaining effectiveness, and is cost-effective compared with empirical dose adjustments based on bedside serum liver biochemistry. Commonly, recruitment of patients to these trials can be difficult, although appropriate patients are commonly seen in general oncology practice.

Until then, clinicians will be reluctant to change practice. Chemotherapy dosing based on body surface area has been the mainstay of cancer treatment for several decades. Although serum liver biochemistry is commonly regarded as a marker or predictor of possible metabolic aberration, and although appropriate trials for safer use of chemotherapy in the setting of biochemical abnormalities continue to be done, current biochemical tests are not an adequate assessment of liver metabolic function.
In the future, alternative assessments will likely be used to individualise chemotherapy dosing for a particular patient’s metabolic capacity. Data from phase III clinical trials are mainly based on dosing according to body surface area, and it is understandable that clinicians and regulatory agencies might be reluctant to move away from these strategies. However, these studies commonly exclude patients with liver impairment, those who are obese, or elderly people—ie, individuals who need the tailored dosing that is desired.

Conflicts of interest
The authors declared no conflicts of interest.

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