

# Dose recommendations for anticancer drugs in patients with renal or hepatic impairment



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Renal or hepatic impairment is a common comorbidity for patients with cancer either because of the disease itself, toxicity of previous anticancer treatments, or because of other factors affecting organ function, such as increased age. Because renal and hepatic function are among the main determinants of drug exposure, the pharmacokinetic profile might be altered for patients with cancer who have renal or hepatic impairment, necessitating dose adjustments. Most anticancer drugs are dosed near their maximum tolerated dose and are characterised by a narrow therapeutic index. Consequently, selecting an adequate dose for patients who have either hepatic or renal impairment, or both, is challenging and definitive recommendations on dose adjustments are scarce. In this Review, we discuss the effect of renal and hepatic impairment on the pharmacokinetics of anticancer drugs. To guide clinicians in selecting appropriate dose adjustments, information from available drug labels and from the published literature were combined to provide a practical set of recommendations for dose adjustments of 160 anticancer drugs for patients with hepatic and renal impairment.

## Introduction

Renal and hepatic impairment are common pathologies in the general population. In 2017, the global prevalence of liver diseases was estimated to be approximately 1·5 billion and chronic kidney disease to be approximately 0·7 billion.<sup>1</sup> Cancer is also a major contributor to the global disease burden, affecting 100 million individuals worldwide.<sup>1</sup> All three diseases show an increased prevalence because of ageing populations and new treatments that prolong survival, which occurs more often in high-income settings. Furthermore, the incidence of renal or liver impairment, or both, in patients with cancer will be even larger because of the direct result of the disease itself, or as a result of previous nephrotoxic or hepatotoxic treatments. Earlier research has shown that approximately 55% of patients with cancer had an estimated glomerular filtration rate of less than 90 mL/min and approximately 15% of patients had an estimated glomerular filtration rate of less than 60 mL/min.<sup>2</sup> For hepatic impairment, to the best of our knowledge, specific prevalence data for patients with cancer are currently absent. Most anticancer drugs are characterised by a narrow therapeutic index. Historically, anticancer drugs are dosed near the maximum tolerated dose on the basis of body surface area. For newer, oral anticancer drugs and some monoclonal antibodies, a fixed-dose approach is used. In the late 1950s, the idea that dosing based on body surface area corrects for differences in pharmacokinetic parameters, such as clearance, was introduced, which is surprising because most body surface area dosing of anticancer drugs does not reduce the interindividual variability in pharmacokinetics and thereby pharmacodynamics.<sup>3</sup> Moreover, this approach does not account for other factors that might influence a drug's pharmacokinetics, such as renal and hepatic function. The pharmacokinetic profile of a drug for individuals with renal or hepatic impairments could lead to either increased or decreased drug exposure, necessitating dose adjustments. Understanding the effect

of these pharmacokinetic changes on the disposition of specific anticancer drugs is essential for selecting the appropriate starting dose, aiming for maximal efficacy, and avoiding unnecessary toxicity. Despite the high prevalence of patients with renal or hepatic impairment, data on the pharmacokinetics of anticancer drugs in patients with renal or hepatic impairment are scarce. Although general recommendations for dosing anticancer drugs in patients with renal or hepatic impairment have been provided by the European Society of Medical Oncology,<sup>4,5</sup> this information is often difficult to gather, as it is spread out from a wide variety of sources and is often difficult to translate into specific dose adjustment recommendations. In light of this point, this Review aims to aid clinicians by providing dose recommendations for anticancer drugs in patients with varying degrees of renal or hepatic impairment. These dose recommendations are based on available evidence from published literature, information from drug labels, and extrapolations based on pharmacokinetic properties of the drug. Furthermore, this Review discusses the main pharmacokinetic changes in patients with renal or hepatic impairment.

## Data collection

### Drug selection

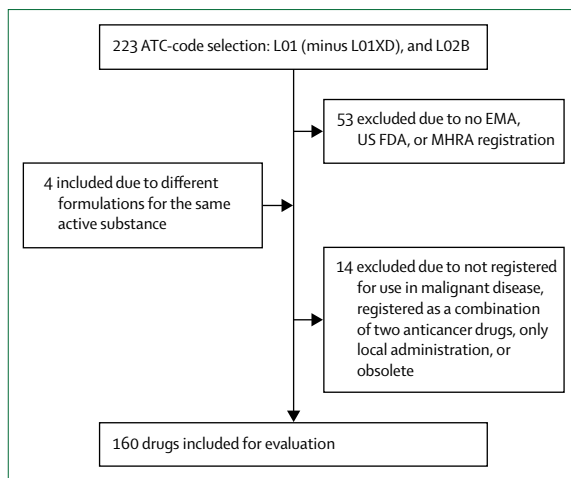
Anticancer drugs of interest for both solid tumours and haematological malignancies were identified by searching the WHO Collaborating Centre for Drug Statistics Methodology index for drugs with Anatomical and Therapeutic Chemical code L01 (antineoplastic agents) and L02B (hormone antagonist and related agents). Category L01XD (sensitisers used in photodynamic or radiotherapy) was excluded from this Review. Subsequently, only those anticancer drugs with US Food and Drug Administration (FDA), European Medicines Agency (EMA), or the UK Medicines and Healthcare products Regulatory Agency registration until Sept 1, 2018, were included. Anticancer drugs with a

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See Online for appendix



**Figure: Flowchart of anticancer drug selection**

ATC=Anatomical Therapeutic Chemical. EMA=European Medicines Agency. FDA=Food and Drug Administration. MHRA=Medicines and Healthcare products Regulatory Agency.

similar Anatomical and Therapeutic Chemical code, but with an alternative formulation (eg, liposomal) beside the conventional formulation were also added to the selection. Anticancer drugs were excluded if they were either not registered for use in malignant disease; registered as a combination of two anticancer drugs; only locally administered; or were deemed obsolete (ie, no longer used in current practice; figure).

### Evidence synthesis

For all specific anticancer drugs, FDA labels and summary of product characteristics were searched for information concerning the pharmacokinetics and dosing recommendations in patients with renal or hepatic impairment (including dose recommendations for patients receiving haemodialysis).

Dose recommendations were formulated using the following three algorithms: first, for anticancer drugs of which renal or hepatic impairment data were available from registration studies or from dedicated pharmacokinetic studies done in patients with renal or hepatic insufficiency, the information was directly translated to the specific recommendations formulated; second, for anticancer drugs of which data for mild or moderate renal or hepatic impairment were available, but data for severe function impairment were absent, the recommendations for severe impairment were made by extrapolation. By formulating the recommendation for these drugs, the reported effect in mild or moderate organ impairment on drug exposure and the contribution of the liver and kidney in the metabolism and elimination of the specific drug were taken into consideration. And third, for anticancer drugs of which no data were available from registration studies or from dedicated studies done in patients with organ impairment, the metabolic pathway of the drug was used for evaluation of

the contribution of the liver and kidney in metabolism, and elimination and extrapolations were made based on this information.

The involvement of the kidney and liver in anticancer drug metabolism and elimination is specified in the appendix. A detailed description of the enzymes and transporters involved in the metabolism of each drug is not specified because these details are beyond the scope of this Review.

### Findings

We identified a total of 160 eligible anticancer drugs. In the appendix, all the anticancer drugs are listed in alphabetical order with specific dosing recommendations. In the panel, anticancer drugs for which a dose adjustment is necessary in renal impairment, haemodialysis, or hepatic impairment are listed.

### Renal impairment

#### Measurements of renal impairment

Renal clearance of a drug is determined by the sum of three different processes; glomerular filtration, tubular secretion, and tubular reabsorption. Renal function is usually expressed as estimated glomerular filtration rate on the basis of creatinine clearance. Measuring the actual glomerular filtration rate, with the isotopic marker  $^{51}\text{Cr}$ -EDTA, is considered the gold standard in patients with cancer. However, this approach is not routinely used in practice because of its high costs and labour intensity. Different methods exist for measuring (eg, 24 h urine test) and estimating glomerular filtration rate (eg, Cockcroft and Gault formula, Modification of Diet in Renal Disease study equation, or Chronic Kidney Disease Epidemiology Collaboration formula [CKD-EPI]). Present guidelines recommend the use of the CKD-EPI formula for optimal estimation of the glomerular filtration rate.<sup>8,9</sup> Specific guidelines for pharmacokinetic studies in patients with renal impairment have been given by both the FDA and the EMA.<sup>10,11</sup> In these guidelines, the use of the estimated glomerular filtration rate is a sufficient measure for renal function in pharmacokinetic studies. Of note, renal drug clearance might also be affected by processes other than glomerular filtration, such as tubular secretion and reabsorption. However, hardly any clinical data are available for these processes. Therefore, for the purposes of this Review, we use the estimated glomerular filtration rate as a measure for renal function to guide dose recommendations.

#### Dose adjustment for renal impairment

For anticancer drugs that are eliminated, or partly eliminated, via the kidneys, diminished renal function might decrease their or their metabolites' excretion. This decreased excretion might lead to drug accumulation and increased exposure, which could result in toxicity. Only a small number of anticancer drugs are almost exclusively eliminated unchanged by the kidneys, such

as platinum compounds and folic acid antagonists. In patients with renal impairment, therefore, a dose reduction would be expected for these drugs directly proportional to the percentage decrease in the glomerular filtration rate. For carboplatin, a clear relationship exists between carboplatin exposure and glomerular filtration rate.<sup>12</sup> However, for other platinum compounds and folic acid antagonists, the relationship between drug exposure and renal function is less apparent.<sup>13–17</sup> Some of these drugs are contraindicated in patients who have more severe renal impairment, because of the narrow therapeutic window or profound toxicity, including nephrotoxicity.

For most anticancer drugs, biotransformation, at least partly, takes place in the liver, on which the more water-soluble metabolites can be renally excreted. For these drugs, the required dose adjustments are more complex to predict. Anticancer drugs with a wider therapeutic index, or with large inter-individual variability, might not directly need a dose adjustment (eg, exemestane).<sup>18</sup> Furthermore, some drugs can be cleared through upregulation of their non-renal routes of elimination, which compensates for the loss in renal clearance. For example, this process applies to the histone deacetylase inhibitor panobinostat, of which the parent compound and its metabolites are almost equally excreted in faeces and urine.<sup>19</sup> In a phase 1 study<sup>19</sup> in patients with mild (estimated glomerular filtration rate of 50–79 mL/min) and moderate (estimated glomerular filtration rate of 30–49 mL/min) renal impairment, no statistically significant difference was observed in panobinostat exposure compared with patients with normal renal function. Adequate renal function is also essential for the excretion of inactive but toxic metabolites. For this reason, ifosfamide should not be administered in patients with renal impairment because accumulation of the chloroacetaldehyde metabolite causes encephalopathy and is directly toxic to the tubular cells and hinders further ifosfamide clearance.<sup>20</sup> Monoclonal antibodies form a subset of anticancer drugs with very distinct pharmacokinetics, because they do not depend on renal or hepatic function for their clearance. Monoclonal antibodies are subject to proteolytic catabolism and intracellular degradation after binding to their target, hence no need for dose adjustment is expected in case of renal or hepatic impairment.<sup>21</sup> Therefore, EMA and FDA guidelines state that no studies are required to confirm the absence of effect of hepatic and renal impairment on the pharmacokinetics of monoclonal antibodies.<sup>10,11</sup>

However, for antibody–drug conjugates the elimination pathway of the linked cytotoxic compound must be considered. An example is brentuximab vedotin. This antibody–drug conjugate consists of a chimeric anti-CD30 monoclonal antibody linked to the cytotoxic monomethyl auristatin E. Monomethyl auristatin E is predominantly excreted unchanged in faeces and to

#### **Panel: Anticancer drugs that require dose adjustments in patients with haemodialysis or renal or hepatic impairment**

Renal impairment is defined as a glomerular filtration rate below 60 mL/min. Haemodialysis is defined as the use of conventional haemodialysis. Hepatic impairment is categorised according to Child-Pugh score or the National Cancer Institute Organ Dysfunction Working Group.<sup>6,7</sup> Specific dose recommendations, the supporting evidence, the metabolic pathway of the anticancer agents, and references are summarised in the appendix. For mild or moderate hepatic impairment, anticancer drugs are presented that require dose adjustment in mild or moderate hepatic impairment. For these agents, dose adjustments for severe hepatic impairment are also required.

#### **Renal impairment or haemodialysis, or both**

Amsacrine, arsenic trioxide, bleomycin, bosutinib, brentuximab vedotin, brigatinib, busulfan, capecitabine, carboplatin, carmustine, cisplatin, cladribine, clofarabine, crizotinib, cyclophosphamide, cytarabine (high dose  $\geq 1$  g/m<sup>2</sup>), dacarbazine, daunorubicin, decitabine, doxorubicin, eribulin, etoposide, fludarabine, hydroxycarbamide, idarubicin, ifosfamide, irinotecan, ixazomib, lenvatinib, lomustine, melphalan, mercaptopurine, methotrexate, mitomycin, olaparib, oxaliplatin, pemetrexed, pentostatin, pralatrexate, procabazine, raltitrexed, ruxolitinib, sorafenib, streptozocin, sunitinib, tegafur–gimeracil–oteracil, thiotepe, topotecan, treosulfan, vandetanib, and vinflunine.

#### **Mild or moderate hepatic impairment**

Abiraterone, amsacrine, axitinib, belinostat, bendamustine, binimetinib, bortezomib, bosutinib, brentuximab vedotin, brigatinib, cabazitaxel, cabozantinib, carfilzomib, chlormethine, cladribine, crizotinib, dabrafenib, daunorubicin, docetaxel, doxorubicin, liposomal doxorubicin (Myocet; Teva, Haarlem, Netherlands), pegylated liposomal doxorubicin (Doxil and Caelyx; Janssen-Cilag International, Beerse, Belgium), enasidenib, encorafenib, epirubicin, eribulin, erlotinib, everolimus, flutamide, fulvestrant, gefitinib, gemcitabine, ibrutinib, idarubicin, irinotecan, ixabepilone, ixazomib, mercaptopurine, nintedanib, nab–paclitaxel, paclitaxel, panobinostat, pazopanib, ramucirumab, ribociclib, romidepsin, ruxolitinib, temsirolimus, thiotepe, tivozanib, trabectedin, trametinib, vinflunine, and vorinostat.

#### **Only for severe hepatic impairment**

Abemaciclib, alectinib, anastrozole, arsenic trioxide, asparaginase, azacitidine, busulfan, carmustine, ceritinib, chlorambucil, clofarabine, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, etoposide, fluorouracil, idelalisib, ifosfamide, lapatinib, lenvatinib, letrozole, lomustine, methotrexate, midostaurin, mitomycin, mitotane, mitoxantrone, neratinib, nilutamide, olaparib, osimertinib, palbociclib, pemetrexed, pixantrone, raltitrexed, regorafenib, sorafenib, tamoxifen, teniposide, topotecan, toremifene, trastuzumab emtansine, vemurafenib, vinblastine, vincristine, liposomal vincristine, and vinorelbine.

a lesser extent in urine. In a phase 1 study<sup>22</sup> with brentuximab vedotin, a 1.9–times increase in exposure was observed for monomethyl auristatin E in patients with severe renal impairment (defined as a creatinine clearance of less than 30 mL/min) compared with patients with normal renal function.

Moreover, for drugs that are predominantly cleared by the liver and for which there is presumably no need to adjust the dose in renal impairment, interesting pharmacokinetic changes can occur in patients with end-stage renal impairment. In patients with renal insufficiency, especially in those with end-stage

renal disease, several physiological changes have been described that also influence non-renal clearance. These changes include alterations in plasma protein binding, decreased activity of drug-metabolising enzymes, and alterations in the activity of uptake and efflux transporters.<sup>23,24</sup> Accumulation of uraemic toxins has been proposed as a possible cause for these effects, as these changes are mitigated in patients undergoing dialysis.<sup>25</sup> Likewise, an effect of renal impairment on the exposure of anticancer drugs with predominant hepatic metabolism and excretion has been observed, for instance with imatinib. In a phase 1 study,<sup>26</sup> a substantially higher total exposure (indicated by the area under the concentration–time curve) of imatinib was observed in patients with mild (creatinine clearance 40–59 mL/min), moderate (creatinine clearance of 20–39 mL/min), and severe (creatinine clearance <20 mL/min) renal impairment.<sup>26</sup> As the excretion of imatinib in urine is less than 13%, this effect was unexpected. The increase in exposure might be explained by a decreased activity of hepatic metabolic enzymes, resulting in a decreased imatinib clearance. Another explanation might be the up-regulation of acute phase proteins, such as alpha-1-acid glycoprotein (AAG), which has been documented both in patients with cancer and those with renal impairment.<sup>24,27</sup> AAG is a plasma protein for which basic drugs, such as imatinib, generally have high affinity towards.<sup>27</sup> For imatinib, the increase in total drug levels might have been caused by an increase in AAG concentrations. However, further research is necessary to confirm this hypothesis and to elucidate the underlying causes of these pharmacokinetic alterations in patients with severe renal impairment.

Another important condition caused by chronic renal disease and cancer is hypoalbuminaemia.<sup>24,27</sup> As less protein is available for drug binding, the unbound fraction of a drug might increase. As additional fractions of a free drug are subject to elimination, a new equilibrium might be formed with similar unbound drug levels (if drug clearance is unaffected). However, if hypoalbuminaemia coexists with impaired drug clearance, unbound drug levels will increase. This effect is important as unbound drugs can exert efficacy but also drug toxicity.

In addition to pharmacokinetic changes, renal impairment might alter patients' sensitivity to anticancer drugs even if drug exposure is unaffected. An example is the increased toxicity of sorafenib observed in the study by Miller and colleagues<sup>28</sup> in patients with varying degrees of renal impairment, although sorafenib exposure was not altered. In conclusion, renal impairment not only affects renal excretion of active compounds and metabolites, but can also influence drug absorption, distribution, or metabolism. In addition, the exposure–toxicity relation for anticancer drugs might be altered in these patients (panel).

## Haemodialysis

Information on the influence of haemodialysis on the pharmacokinetics of anticancer drugs is usually found only in case reports or small case series. Most of these publications discuss the effect of conventional haemodialysis on anticancer drugs. Lately, the use of intermittent online haemodiafiltration and high-flux haemodialysis is increasing.<sup>29,30</sup> For these newer techniques, even less information is available on the effect these techniques have on the pharmacokinetics of anticancer drugs. Drug clearance in patients undergoing haemodialysis is determined by drug characteristics (eg, protein bound fraction, molecular weight, and volume of distribution), dialysis characteristics (eg, pore size and flow rates), and patient characteristics (eg, albumin level and residual kidney function). For anticancer drugs that are excreted renally, a dose adjustment is often needed in patients receiving haemodialysis. Haemodialysis enables the administration of some anticancer drugs in patients who would otherwise be ineligible for treatment because of insufficient renal elimination of an active or toxic moiety. This scenario is illustrated by a case describing the administration of a high dose of methotrexate (7.2 g/m<sup>2</sup>) in a patient who was functionally anephric.<sup>31</sup> Daily intermittent high-flux haemodialysis yielded a total body clearance comparable to those patients who had unimpaired renal function.<sup>31</sup>

Most reviewed anticancer drugs are highly protein bound, and therefore unlikely to be dialysed by conventional haemodialysis. The same is the case for anticancer drugs that are predominantly cleared by the liver.

As emphasised earlier, renal impairment might alter other pharmacokinetic processes that might demand a dose adjustment. An interesting example was published by Khosravan and colleagues.<sup>32</sup> In their phase 1 study, no clinically relevant differences in sunitinib and its active metabolite SU12662 exposure were observed in patients with severe renal impairment (creatinine clearance of <30 mL/min) compared with participants who had normal renal function. Yet, in patients with end-stage renal disease requiring haemodialysis, a 47% lower exposure of sunitinib and SU12662 was observed.<sup>32</sup> Since sunitinib is not removed by haemodialysis, the authors suggested that the decrease in exposure was probably a result of lower drug absorption.<sup>23</sup>

## Hepatic impairment

### Measurements of hepatic impairment

For liver function, a general index comparable to estimated glomerular filtration rate for kidney function, does not exist. The FDA and EMA recommend the use of the Child-Pugh scoring system for studies investigating the effect of hepatic impairment.<sup>33,34</sup> The Child-Pugh score is a composite score of bilirubin, albumin, and prothrombin levels together with the presence or absence of encephalopathy and ascites.<sup>6</sup> Although the Child-Pugh score was originally developed to predict operative

mortality in patients with liver cirrhosis, it is now frequently used as a scale for assessing hepatic impairment. The FDA and EMA guidelines note the importance of verifying that alterations in Child-Pugh components are the result of liver disease, and are not caused by some other underlying disease such as cancer.<sup>33,34</sup> The National Cancer Institute Organ Dysfunction Working Group recommends grading liver dysfunction as either mild, moderate, or severe, on the basis of the total bilirubin and transaminases concentrations, in which bilirubin contributes most to metabolic capacity. Most studies that were evaluated for this Review used either one of these grading systems. However, the results from these different grading systems are not interchangeable and are difficult to compare with one another. Therefore, multiple hepatic impairment descriptions are presented in our specific dose recommendations. Table 1 outlines the classification of the Child-Pugh score and table 2 outlines the National Cancer Institute Organ Dysfunction Criteria for Liver Impairment.<sup>6,7,34</sup>

### Dose adjustment for hepatic impairment

For most anticancer drugs, the liver is the main organ for drug metabolism and excretion. For patients with cancer, impaired liver function is most commonly caused by liver metastases but could also be due to other causes, such as hepatotoxicity of previous (anticancer) treatments, cirrhosis, or hepatitis.<sup>35</sup> Drug biotransformation in the liver is essential for both detoxification of active compounds and toxic metabolites as well as activation of prodrugs. Therefore, reduced metabolic capacity can have a profound effect on the exposure of anticancer drugs. To illustrate, everolimus, which is predominantly hepatically metabolised, showed a gradual increase in exposure with increasing Child-Pugh score.<sup>36</sup> For this reason, a dose adjustment for everolimus in these patients is required to prevent overexposure. For anticancer drugs that rely on hepatic metabolism to form their active metabolites, such as cyclophosphamide, exposure to the active metabolites might be decreased in patients with hepatic impairment. For example, in patients with severe liver impairment, the clearance of cyclophosphamide was significantly decreased and less toxicity was observed.<sup>37</sup> This finding implies that fewer active metabolites are formed and, consequently, treatment might be less effective in these patients. Reduced metabolic capacity can be the direct result of the loss of functional hepatocytes or can be an indirect result due to alterations in the activity of drug metabolising enzymes and drug transporters.<sup>38,39</sup> A decreased activity of cytochrome P450 3A4 has been reported in patients with cancer with an acute-phase inflammatory response.<sup>40</sup> However, present serum liver biochemical tests are not an adequate assessment of liver metabolic capacity.<sup>35</sup> For instance, liver metastases and many non-malignant causes might also disrupt liver biochemistry tests, apart from the degree of alteration in metabolic capacity.<sup>38,39</sup>

	1 point	2 points	3 points
Total bilirubin (mg/dL)	<2	2–3	>3
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (sec prolonged) or INR	<4 or <1.7	4–6 or 1.7–2.3	>6 or >2.3
Ascites	Absent	Slight	Moderate
Encephalopathy (grade)†	None	1 or 2	3 or 4

INR=international normalised ratio. \*Child-Pugh classification is obtained by adding the score for each parameter. Grade A (mild)=5–6 points. Grade B (moderate)=7–9 points. Grade C (severe)=10–15 points. †Grade 0: normal consciousness, personality, neurological examination, and electroencephalogram. Grade 1: restless, sleep disturbed, irritable or agitated, tremor, and impaired handwriting, five cycles per s (cps) waves. Grade 2: lethargic, time-disoriented, inappropriate, asterix, ataxia, slow triphasic waves. Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, and slower waves. Grade 4: unarousable coma, no personality or behaviour, decerebrate, and slow 2–3 cps delta activity.

**Table 1: Child-Pugh score by clinical and lab criteria**<sup>6,34</sup>

	Total bilirubin	Alanine aminotransferase or aspartate aminotransferase
Mild	B1: ≤ULN; B2: >1–1.5×ULN	B1: >ULN; B2: Any
Moderate	>1.5–3×ULN	Any
Severe	>3×ULN	Any

Group B (mild) is defined according to either of two criteria (B1 or B2). ULN=upper limit of normal.

**Table 2: Classification of hepatic impairment by the National Cancer Institute Organ Dysfunction Working Group**<sup>7</sup>

Moreover, results of clinical studies in patients with hepatic impairment by the Child-Pugh scoring system might not be translatable to patients with cancer and liver metastases. For instance, liver disease without cirrhosis, but with changes in liver biochemistry tests, is considered to cause only mild alterations in drug pharmacokinetics.<sup>41</sup>

The importance of the aetiology of hepatic impairment has been shown in a study with gefitinib, in which Horak and colleagues<sup>42</sup> observed no clinically relevant differences in exposure for patients with moderate and severe hepatic impairment due to liver metastases. However, a significant increase in gefitinib exposure was found in patients with Child-Pugh score of B and C due to cirrhosis.<sup>42</sup>

Next to the decreased metabolising capacity, alterations in biliary excretion, liver blood flow, and plasma protein binding might also occur in patients with liver impairment. Obstruction of biliary excretion might lead to drug accumulation, which subsequently might cause hepatocellular damage.<sup>39</sup> In addition, changes in liver blood flow will mainly affect drugs with a high hepatic extraction ratio. Moreover, impaired production of albumin and AAG might lead to an increase in unbound fraction. An example of a highly protein-bound anticancer drug with a high hepatic extraction ratio is ibrutinib.



### Search strategy and selection criteria

PubMed and official drug registration documentation as published by the responsible authorities (US Food and Drug Administration [FDA] and European Medicines Agency [EMA] or UK Medicines and Healthcare products Regulatory Agency) were searched between July 1 and Nov 15, 2018. The latest official prescribing information as released by the FDA was retrieved from the FDA website. The latest summary of product characteristics was retrieved on the Medicines and Healthcare products Agency of the United Kingdom website or from the European Public Assessment Report on the EMA website. If different generic versions of the anticancer drugs were available, the label or Summary of Product Characteristics concerning the originally registered product was used. For the literature search (done between July 1 and Nov 15, 2018), a search strategy combining synonyms of renal impairment, hepatic impairment, and the specific drug name was used in the PubMed database (appendix). For drugs with limited data available, the citations of peer-reviewed articles were checked for additional information. From the PubMed searches, studies and case reports investigating the drug of interest in patients with renal impairment, hepatic impairment, or on haemodialysis containing pharmacokinetic data were selected. Articles without pharmacokinetic data but with relevant information on tolerability or efficacy were included if deemed of added value. When multiple articles or case reports covered the same area and were showing the same data, the most relevant article, as judged by two authors (SDK and GL) was selected. Only articles published in English were reviewed. Studies that solely reported on drug-induced renal or hepatic failure in patients without pre-existing renal or hepatic impairment were excluded.

De Jong and colleagues<sup>43</sup> observed an increase in total ibrutinib exposure in patients with impaired albumin production of 2·7 times for Child-Pugh A, 8·0 times for Child-Pugh B, and 9·5 times for Child-Pugh C. However, for unbound ibrutinib, this effect was even more prominent, with an increased exposure of 4·4 times for Child-Pugh A, 9·6 times for Child-Pugh B, and 13·1 times for Child-Pugh C.<sup>43</sup> Apart from pharmacokinetic changes, hepatic impairment might also alter patients' individual tolerability, for instance with pazopanib, which is registered at a dose of 800 mg once daily. In patients with moderate and severe hepatic impairment, the maximum-tolerated dose was 200 mg, although plasma drug levels were significantly decreased.<sup>44</sup>

In conclusion, hepatic impairment might reduce the metabolising capacity, biliary outflow, or liver blood flow and plasma protein levels, which might lead to increased exposure to the parent compound. For prodrugs, this course could lead to a decrease in exposure of active moieties. Therefore, understanding the metabolic pathway of the drug and resulting pharmacokinetic changes are essential in making dose decisions (panel).

### Discussion

Selecting the right dose for each line of therapy for patients with cancer with renal or hepatic impairment is a challenging task for clinicians. The number of clinical studies that have data from patients with hepatic or renal impairment is scarce. Moreover, these studies often only include a small, and therefore rare, subset of patients, which makes it difficult to extrapolate the results into clinical practice. The choice between the prudent approach of using dose reductions with possible risk of underexposure and the somewhat bold use of full-dose regimens with possible risk of toxicity is a difficult trade off. The decision for either approach also strongly relies on the intent of treatment (ie, curative or palliative). Therefore, risk-benefit assessments must be made for each patient on an individual basis. Besides renal and hepatic impairment, many other known factors exist that influence drug exposure and safety, which also should be considered. These factors include, for instance, cachexia, smoking status, potential drug–drug interactions, and genetic variability.<sup>35,45</sup>

Most anticancer drugs are used in combinations that are proven safe and effective. The aim of adjusting the starting dose of specific drugs for patients who might have organ failure is to reach drug exposure levels similar to patients who have normal organ function and who are investigated in registration trials (appendix).

This Review focuses solely on dose adjustments at the start of each line of anticancer therapy in adult patients. Further individualisation after treatment initiation depends on both a patient's individual response and tolerability (eg, drug-induced renal or hepatic impairment). For drugs with a predefined target exposure level or established therapeutic ranges, concentration measurements might enable further optimisation of the dosing regimen. Particularly for anticancer drugs taken daily, such as oral small-molecular tyrosine kinase inhibitors, therapeutic drug monitoring should be considered early after initiation of therapy.<sup>46</sup> The guidelines for studies in patients with renal and hepatic impairment issued by the FDA and EMA were a major step forward in formulating dose recommendations for these patients. For newly registered anticancer drugs, dose recommendations are provided for patients with mild and moderate renal and hepatic impairment. Nevertheless, dose recommendations for patients with severe renal or hepatic impairment are often scarce. Therefore, it would be helpful to collect the pharmacokinetics, efficacy, and safety of anticancer drugs data of patients with cancer who have renal or hepatic impairment. These data will enable us to make more informed decisions at the start of therapy for patients who might benefit most from tailored dosing.

### Conclusion

This Review discusses the main concerns and the underlying pharmacokinetic changes relevant for

selecting an appropriate starting dose for anticancer drugs in the presence of renal or hepatic impairment. The authors provide a comprehensive overview of the evidence from published literature and formulated practical recommendations for each anticancer drug. In general, the amount of clinical pharmacokinetics studies of patients with cancer and renal or hepatic impairment is scarce. Moreover, this information is often difficult to collect as it is spread-out over a wide variety of sources. Therefore, selecting the optimal dose at the start of treatment for patients with renal or hepatic impairment remains a complex challenge for clinicians. With our Review, we aim to provide clinicians a tool to aid dosing decisions at the start of therapy for patients with hepatic and renal impairment.

#### Contributors

NPvE, DMB, FGAJ, NAGL, CMLvH, IMED, and SDK came up with the concept and design of the Review. SDK and GL collected the data, summarised the data in tables, and made extrapolations into specific dosing recommendations when required. The summary was independently reviewed by NPvE. SDK, GL, and NPvE were responsible for data interpretation. SDK and GL wrote the first draft of the manuscript with assistance from NPvE. NPvE, DMB, FGAJ, NAGL, GL, CMLvH, and IMED were responsible for critical revision of the manuscript and data interpretation. All authors gave final approval of the version to be submitted.

#### Declaration of interests

FGAJ has been on an advisory board for Amgen and Servier. DMB has received research grants from Janssen, Merck, ViiV Healthcare, and Bristol-Myers Squibb, has been on an advisory board for Janssen, Merck, AbbVie, ViiV Healthcare, Bristol-Myers Squibb, and Gilead, and received honoraria from Janssen, Merck, AbbVie, ViiV Healthcare, Bristol-Myers Squibb, and Gilead. NPvE has received research grants from Novartis, Astellas, Janssen-Cilag, Gilead, Bristol-Myers Squibb, Pfizer, Roche, AstraZeneca, Ipsen, and Sanofi. CMLvH has received research grants from AstraZeneca, Bristol Meyers Squibb, Merck Sharp and Dohme, Merck, Ipsen, Sanofi, and Novartis. The other authors declare no conflicts of interest.

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