REVIEW ARTICLE

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Dose Adaptation of Antineoplastic Drugs in Patients with Liver Disease

Lydia Tchambaz,[1] *Chantal Schlatter*,[1] *Max Jakob*,[1] *Anita Krâhenbûhl*,[1] *Peter Wolf*[2] and *Stephan Krâhenbûhl*[1]

1 Division of Clinical Pharmacology & Toxicology, University Hopsital, Basel, Switzerland
2 Hospital Library, University Hospital, Basel, Switzerland

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Abstract

Dose adaptation for liver disease is important in patients treated with antineoplastic drugs because of the high prevalence of impaired liver function in this population and the dose-dependent, frequently serious adverse effects of these drugs. We classified the antineoplastic drugs marketed in Switzerland at the end of 2004 according to their bioavailability and/or hepatic extraction to predict their kinetic behaviour in patients with decreased liver function. This prediction was compared with kinetic studies carried out with these drugs in patients with liver disease. The studies were identified by a structured, computer-based literature search.

Of the 69 drugs identified, 52 had a predominant extrarenal (in most cases hepatic) metabolism and/or excretion. For 49 drugs, hepatic extraction could be calculated and/or bioavailability data were available, allowing classification according to hepatic extraction. For 18 drugs, kinetic studies have been reported in patients with impaired liver function, with the findings generally resulting in quantitative recommendations for adaptation of the dosage. In particular, recommendations are precise for 16 drugs excreted by the bile (e.g. doxorubicin and derivatives and vinca alkaloids). Validation studies comparing such recommendations with kinetics and/or dynamics of antineoplastic drugs in patients with decreased liver function have not been published.

We conclude that there are currently not enough data for safe use of cyctostatics in patients with liver disease. Pharmaceutical companies should be urged to provide kinetic data (especially hepatic extraction data) for the classification of such drugs and to conduct kinetic studies for drugs with primarily hepatic metabolism in patients with impaired liver function to allow quantitative advice to be given for dose adaptation.

Dose adaptation for patients with liver disease is more difficult to perform than for patients with impaired renal function. The main reason for this statement is that, unlike the creatinine clearance for the kidney, there is no *in vivo* surrogate to predict hepatic drug clearance. Due to the lack of such *in vivo* markers, predictions concerning dose adaptation in patients with liver disease can only be made based on the kinetic properties of the drugs to be administered and on kinetic studies of the drugs in patients with liver disease.[1]

Several reviews have covered this subject during the last few years.[1-5] In these reviews, drugs are listed according to hepatic extraction (E), which is an important determinant of the hepatic clearance of drugs. The hepatic clearance (Cl_{hep}) of a drug can be expressed as (equation 1):

$$Cl_{hep} = \frac{(f_u \times Cl_i) \times Q}{(f_u \times Cl_i) + Q} \quad \text{(Eq. 1)}$$

where Q is the blood flow across the liver, f_u is the unbound fraction (free) of the drug and Cl_i is the intrinsic clearance of the drug. Cl_i represents the maximal capacity of the liver to metabolise a given drug, not taking into account limitations by liver perfusion.[6] Cl_i can therefore reach values which are larger than Q.

The basis of the classifications used can best be understood by considering the extremes of equation 1, namely $(f_u \times Cl_i) >> Q$ or $Q >> (f_u \times Cl_i)$. When $(f_u \times Cl_i) >> Q$, the denominator in equation 1 simplifies to $(f_u \times Cl_i)$, and Cl_{hep} equals (equation 2):

$$Cl_{hep} = Q \quad \text{(Eq. 2)}$$

For these drugs, the liver has a very large metabolic capacity, E is approaching 1 and the blood flow across the liver becomes rate-limiting for hepatic clearance. The drugs are therefore called 'flow-limited', 'high capacity', 'high clearance' or 'high extraction'. Because of their high hepatic extraction, these drugs have a low bioavailability.

Since portal blood flow can be decreased in patients with liver cirrhosis or patients with multiple metastases,[7,8] hepatic clearance of such drugs is decreased in these situations, possibly necessitating a reduction of the maintenance dose. A second potential problem of these drugs is an increase in their bioavailability in patients with porto-systemic shunts. Porto-systemic shunts are usually present in patients with portal hypertension due to liver cirrhosis or fibrosis or, of importance in patients with cancer, in patients with multiple metastases.[9,10] Therefore, when these drugs are administered orally in patients with portal hypertension, the initial and the maintenance doses have to be reduced according to the expected increase in bioavailability and to the decrease in hepatic blood flow. For intravenous administration, only the maintenance dose has to be reduced according to hepatic blood flow. A list of such drugs is given in a recent publication.[1]

For the second type of drugs, $Q >> (f_u \times Cl_i)$, the metabolic capacity of the liver is much lower than blood flow across the liver. Equation 1 therefore simplifies to (equation 3):

$$Cl_{hep} = (f_u \times Cl_i) \quad \text{(Eq. 3)}$$

These drugs are therefore called 'low extraction', 'low clearance' or 'capacity-limited'. They have a low extraction during the first passage across the liver and therefore have a high bioavailability, if bioavailability is not limited by other processes than first pass hepatic metabolism. Since Cl_i decreases for most drugs in patients with liver cirrhosis due to a decrease in the activity of cytochrome P450 (CYP) isozymes[11,12] and/or glucuronyl transferases,[13-15] the maintenance dose of such drugs should generally be decreased in these patients. For drugs with a high binding to albumin (>90%), the situation may be more complex. The f_u and the free concentration of these drugs can increase in patients with a low serum albumin level, e.g. patients with liver cirrhosis or malnourished patients, such as patients with cancer. An increase in the free concentration and/or f_u of these drugs may be associated with increased toxicity and also, as shown in equation 3, with an increased hepatic clearance.[16,17] The actual hepatic clearance of these drugs is therefore difficult to predict in patients with chronic liver disease.

In between these two extremes, there are drugs with an 'intermediate extraction', showing characteristics of both groups. The dosage advice for these drugs in patients with liver cirrhosis is to start with a low dose and to up-titrate carefully to find the correct maintenance dose.

Table I. Classification of liver disease and severity of liver dysfunction

Parameter	Pathophysiological condition and clinical significance	Severity[a]
Alanine aminotransferase level	Breakdown (necrosis or apoptosis) of hepatocytes. Hepatocellular injury[b] if >2 × ULN	Moderate injury: 2–5 × ULN Severe injury: >5 × ULN
Alkaline phosphatase level	Cholestasis[c] if >2 × ULN	Moderate cholestasis: 2–5 × ULN Severe cholestasis: >5 × ULN
Serum bilirubin level	Cholestasis (exclude prehepatic causes)	Moderate: 25–50 μmol/L Severe: >50 μmol/L
Serum albumin level	Impaired hepatic protein synthesis	Moderate: 30–35g/L Severe: <30g/L
Prothrombin activity	Impaired hepatic protein synthesis	Moderate: 40–70% Severe: <40%

a The severity is classified according to Donelli et al.,[20] with some modifications.

b Hepatocellular injury is defined according to Benichou.[21]

c Cholestasis is defined according to Benichou.[21]

ULN = upper limit of normal.

However, regarding dose adaptation in patients with cancer, it has to be recognised that the administration guidelines discussed previously in this section focus on patients with liver cirrhosis or fibrosis and not on patients with increased transaminase levels and/or cholestasis, which are found frequently among patients treated with antineoplastic drugs. Since the majority of antineoplastic drugs are metabolised by the liver and are associated with severe dose-dependent toxicity, the question of whether the dose has to be adapted in a patient with increased transaminase levels and/or cholestasis is important (table I). The most prevalent liver disease in this group of patients is the presence of liver metastases, possibly resulting in cholestasis and/or portal hypertension.[10,18,19] Since many antineoplastic drugs are potentially hepatotoxic themselves, drug-induced liver disease may also be problematic in patients undergoing repetitive cycles of chemotherapy.

Therefore, the aims of the review were to: (i) categorise the antineoplastic drugs according to pharmacokinetic criteria; (ii) compare this categorisation with the dose recommendations in patients with liver disease given in the standard literature; (iii) formulate dose recommendations for dose adaptation; and (iv) localise gaps in the current recommendations.

2. Literature Search Methodology

We searched MEDLINE and EMBASE for studies dealing with dose adaptation and hepatic adverse effects for all antineoplastic drugs that were on the market in Switzerland at the end of 2004. The databases were screened using the following medical subject heading (MeSH) terms: 'antineoplastic agents', 'drug toxicity', 'pharmacokinetics' and 'liver diseases'. The references detected by this search were then hand screened for other suitable papers. In addition to databases, the standard literature was screened for dose-adaptation recommendations and adverse effects on the liver, including the *Swiss Compendium of Drugs*[22] (similar to the *Physicians' Desk Reference*[23]), *Therapeutic Drugs*[24] and *Hepatotoxicity*.[25]

The antineoplastic drugs were categorised according to pharmacokinetic principles as outlined in the previous section and based on the reviews of Huet and Villeneuve[16] and Delco et al.[1] The categorisation system used is based on the level of hepatic extraction, bioavailability or protein binding of the specific drugs (table II). Values for bioavailability and protein binding could be found either in the original articles[20,26-54] or in other sources.[22-24,55,56] For hepatic extraction, data in the literature are rare, making it necessary to estimate extraction from bioavailability (table II) or by the following equation (equation 4):

$$E = \frac{Q_0 \times Cl_{sys}}{Q} \quad \text{(Eq. 4)}$$

where Q_0 is the extrarenal dose fraction (the fraction of a drug that is not excreted unchanged by the kidney), Cl_{sys} is the systemic clearance of the drug (determined in plasma) and Q the plasma flow across the liver. The values for Q_0 and Cl_{sys} were obtained from the literature[22-24,56] and Q was assumed to be 900 mL/min.

Dosage recommendations originate either from the original articles or from the manufacturer as published in the *Physicians' Desk Reference*[23] and/or the *Swiss Compendium of Drugs*.[22]

Drug-induced liver disease was classified according to Benichou[21] and the severity of liver disease according to Donelli et al.[20] (see table I).

3. Literature Search Results

We identified a total of 111 articles that were relevant to our review.[26-54,57-137] In 17 of these, drug metabolism data were reported, 49 contained hepatic adverse effects of antineoplastic agents and 45 were kinetic studies in patients and/or dose-adjustment recommendations.

Data on the 69 antineoplastic drugs on the Swiss market at the end of 2004 have been compiled in to table format and are available from http://pages.uinbas.ch/klinpharm/. From these 69 drugs, 15 fell into category 1, nine fell into category 2 and 25 fell into category 3 (table III). Twenty drugs could not be classified (category 4), demonstrating a lack of data about hepatic extraction and/or bioavailability.

Fifty-two of the 69 drugs have an extrarenal dose fraction (Q_0) value of >0.4 indicating that most antineoplastic drugs are heavily metabolised and/or excreted by the bile. Seven drugs have a Q_0 value of ≤0.4 and for ten drugs, the Q_0 value could not be identified. For 25 drugs, metabolism by the CYP system is important, and 18 drugs are excreted to a significant extent (>5%) by the bile (vinca alkaloids, doxorubicin and derivatives, amsacrine, bicalutamide, dactinomycin, estramustine, exemestan, irinotecan, imitanib, mitoxantrone, paclitaxel and topotecan). For 16 of these drugs, dose-adaptation recommendations are given according to the serum bilirubin level and/or activity of alkaline phosphatase (see table IV). For docetaxel,[20,22] doxorubicin,[112,122-127] idarubicin,[99,100] irinotecan,[102] mitoxantrone,[35-37] paclitaxel,[40-43] topotecan,[56,138] vincristine[139,140] and vinorelbine,[141] these recommendations are based on clinical studies. For amsacrine, bicalutamide, dactinomycin, daunorubicin, imatinib, vinblastine and vindesine, there are general statements in the *Swiss Compendium of Drugs*[22] and/or the *Physicians' Desk Reference*[23] that the dose should be adapted or stopped in patients with decreased liver function. For estramustine and exemestane, there are no recommendations regarding dosage in patients with liver disease. We recommend that these two drugs should be used with caution in patients with cholestasis and that the dose should be adapted according to dose-adapted adverse reactions.

For only 18 of the 69 drugs identified, recommendations for dose adaptation are based on published studies in patients with hepatic dysfunction.[27,28,31-34,40,41,47-52,54,110-120,122-137] For 44 of the 69 drugs, significant adverse effects on the liver have been reported.[26-28,31-34,40,41,47-54,110-137] This is important to realise, rendering drug-induced liver disease an important differential diagnosis in

Table II. Categorisation of antineoplastic drugs screened according to pharmacokinetic variables

Category	Level of hepatic extraction (%)	Resulting oral bioavailability
1	High (>60)	Oral bioavailability is <40% in the case of complete intestinal absorption (or accordingly lower, if intestinal absorption is not complete)
2	Intermediate (30–60)	Oral bioavailability is 40–70% in the case of complete intestinal absorption (or accordingly lower, if intestinal absorption is not complete)
3	Low (<30)	Oral bioavailability is >70% in the case of complete intestinal absorption (or accordingly lower, if intestinal absorption is not complete). In this category, protein binding may be relevant: for drugs with high binding to albumin (>90%), hepatic clearance may increase
4	Unknown	Not known

Table III. Antineoplastic drugs listed by hepatic extraction category

Category	Drugs
1	Capecitabine, cytarabine, docetaxel, doxorubicin, epirubicin, exemestane, fluorouracil, formestane, gemcitabine, idarubicin, medroxyprogesterone, mercaptopurine, mitoxantrone, vinblastine, vinorelbine
2	Bicalutamide, busulfan, cladribine, estramustine, gefitinib, irinotecan, melphalan, paclitaxel, topotecan
3	Aminoglutethimide, anastrozole, bleomycin, carboplatin, chlorambucil, cisplatin, cyclophosphamide, cyproterone, dacarbazine, etoposide, fludarabine, fosfestrol, goserelin, hydroxycarbamide (hydroxyurea), ifosfamide, imatinib, letrozole, leuprorelin, lomustine, methotrexate, temozolomide, thiotepa, toremifene, triptorelin, vincristine
4	Aldesleukin, alemtuzumab, amsacrine, buserelin, cetuximab, chlormethine (mechlorethamine), dactinomycin, daunorubicin, flutamide, megestrol, mitomycin, nimustine, oxaliplatin, raltitrexed, rituximab, tamoxifen, thioguanine, trastuzumab, tretinoin, vindesine

patients with malignant tumours and impaired hepatic function.

4. Discussion

Our review demonstrates that for antineoplastic drugs, there is a discrepancy between the general recommendations of how drugs should be administered to patients with liver disease[1] and the available kinetic data for these drugs. The most important gaps are a lack of information regarding hepatic extraction and of kinetic studies for critical drugs in patients with impaired liver function.

As explained in the introduction, data about hepatic extraction are important for the classification of a specific drug regarding hepatic elimination in patients with chronic liver disease and liver cirrhosis in particular. It is evident that these data are difficult to obtain, especially the determination of hepatic extraction of a drug, necessitating an invasive procedure that is usually not performed before a drug is marketed. Bioavailability is only a surrogate for hepatic extraction, since a low bioavailability can originate from both a high hepatic extraction and/or a low intestinal absorption. For drugs with a low bioavailability (<40%), hepatic extraction should therefore be known, since this parameter is critical for rational drug administration in patients with impaired liver function, as previously discussed. To circumvent this invasive procedure in humans, a possibility would be to obtain data using perfused livers from animals, e.g. pigs. To the best of our knowledge, no data have been published so far comparing hepatic extraction data for critical drugs between animals (such as pigs) and humans. Another possibility is to estimate hepatic extraction using Q_0, systemic drug clearance and hepatic plasma flow (equation 4). The values obtained with this technique are in satisfactory agreement with the bioavailability for most drugs, with some exceptions (see full table on http://pages.unibas.ch/klinpharm/).

Regarding antineoplastic agents, many of these drugs are used intravenously only, which partially explains the lack of data about oral bioavailability. Nonetheless, taking into account the high prevalence of patients with impaired hepatic function among those treated with these types of drugs,[138] these data should be available for all substances on the market.

Kinetic studies have been conducted in two conditions in particular, namely in patients with cholestasis (as suggested by an increased serum bilirubin level) and in patients with hepatic metastases. Regarding cholestasis, studies exist for most antineoplastic drugs with significant biliary elimination (see table IV). These studies resulted in quantitative recommendations for dose adaptation, for example in jaundiced patients according to their serum bilirubin level. However, to the best of our knowledge, these recommendations have not been validated by kinetic and dynamic studies (including the incidence and severity of dose-dependent adverse effects) in such patients. With cholestasis, it remains unclear whether the serum bilirubin level is the best parameter for predicting dose adaptation or whether the serum bile acid level and/or activity of alkaline phosphatase would be more suitable.

Regarding hepatic metastases, only few studies exist and they have generally not resulted in clear dose-adaptation recommendations. Since hepatic metastases can be associated with portal hypertension and possibly porto-caval shunts,[10,18] the situation can be similar to patients with liver cirrhosis. Oral administration of drugs with a high hepatic extraction should therefore be performed cautiously

Table IV. Kinetic data, hepatic adverse effects and dose adjustment recommendations for the use of antineoplastic drugs with a significant biliary excretion (BE) in patients with liver disease

Drug	Cat[a]	Kinetic parameters[b,c,d]	Frequency of hepatic adverse effects[e]	Dose-dependent adverse reactions	Studies performed and dose recommendations
Amsacrine	4	Metabolism: glutathion conjugation, BE >50%[22] Q_0: 1 V_d: 1.40 L/kg $t_{1/2}$: 5h PB: 97%	Sporadic: cholestasis, hyperbilirubinaemia[25]	Myelosuppression, cardiotoxicity (arrhythmia), hypotonia, nausea and vomiting, alopecia, mucositis[22,24]	Recommendation: 50% dose reduction if serum bilirubin level >34 μmol/L.[26] Dose reduction (70% of normal dose) in patients with severe liver disease[22,24]
Bicalutamide	2	Metabolism: oxidation (CYP), glucuronidation, BE 40%[22] Q_0: ≈1 $t_{1/2}$: 139h PB: 98% Cl_{sys}: 500 mL/min E: 0.56	One case of fulminant liver failure[68]	Blocked androgenic action (hot flushes, breast tenderness, gynaecomastia, reduced libido and erectile function), diarrhoea[22-24]	Recommendations: stop treatment if transaminase levels >3 × ULN or in patients with hyperbilirubinaemia[22]
Dactinomycin	4	Metabolism: BE 50–90%[24] Q_0: 0.7 V_d: 12 L/kg $t_{1/2}$: 36h	Rare: hepatocellular injury, steatosis, VOD[25]	Myelosuppression, nausea and vomiting, diarrhoea, mucositis, alopecia[23,24]	Recommendation: 50% dose reduction in patients with hyperbilirubinaemia. Increase gradually while monitoring dose-dependent toxicity[26]
Daunorubicin	4	Metabolism: reduction, BE 40%[24] Q_0: 0.9 V_d: 40 L/kg $t_{1/2}$: 27h	Rare: VOD when combined with radiation[25]	Myelosuppression, nausea and vomiting, mucositis, alopecia, cardiotoxicity, diarrhoea[23,24]	Recommendation: 25% dose reduction if serum bilirubin level 20–50 μmol/L, 50% dose reduction if serum bilirubin level >50 μmol/L [22,24]
Docetaxel	1	Metabolism: oxidation (CYP3A4).[24] BE 75%, 10% as intact drug[22,24] Q_0: 1 V_d: 1.6 L/kg $t_{1/2}$: 11h PB: 95% Cl_{sys}: 650 mL/min E: 0.72		Myelosuppression, nausea and vomiting, diarrhoea, sensory neuropathy, mucositis, alopecia, fluid retention syndrome[23,24]	Studies: population kinetic studies show a 25% reduction of clearance in patients with transaminase levels >1.5 × ULN and alkaline phosphatase level >2.5 × ULN. In patients with moderate liver injury/cholestasis, clearance was reduced by 27%[22,24] Recommendation: 25% dose reduction if transaminase levels >1.5 × ULN or alkaline phosphatase level >2.5 × ULN. Docetaxel should not be administered if serum bilirubin level is increased or transaminase levels >3.5 × ULN or alkaline phosphatase level >6 × ULN[22,24]

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Table IV. Contd

Drug	Cat[a]	Kinetic parameters[b,c,d]	Frequency of hepatic adverse effects[e]	Dose-dependent adverse reactions	Studies performed and dose recommendations
Doxorubicin	1	Metabolism: reduction to doxorubicinol, sulfation, glucuronidation, BE 50%[20,24] Q_0: 0.95 V_d: 17 L/kg $t_{1/2}$: 26h PB: 80% F: 5% Cl_{sys}: 1150 mL/min E: ≈1	Rare: in combination with etoposide, cyclophosphamide and cisplatin cholestasis and VOD[25]	Myelosuppression, nausea and vomiting, mucositis, alopecia, cardiotoxicity[23,24]	Studies: in five patients with disseminated sarcoma, myelotoxicity and doxorubicin serum levels correlated with hyperbilirubinaemia.[114] In patients with hepatocellular carcinoma, myelotoxicity and serum doxorubicin/doxorubicinol levels correlated with hyperbilirubinaemia.[115,116] In 17 patients with liver metastases and moderate liver disease, kinetics of doxorubicin were not changed but the half-life of doxorubicinol increased.[117] In four patients with moderate liver disease, the half-life of doxorubicin was doubled.[118] In patients with liver metastases and a mild increase in transaminase or alkaline phosphatase levels, the kinetics and toxicity of doxorubicin were not changed[115,116,119,120] Recommendation: 50% dose reduction if serum bilirubin level 20–50 μmol/L. 75% dose reduction if serum bilirubin level >50 μmol/L.[22,24,26,121] Donelli et al.[20] advise dose reduction only if serum bilirubin level is >50 μmol/L
Idarubicin	1	Metabolism: oxidation, BE 8–17%[64,66] Q_0:≈1 $t_{1/2}$: 15.2h PB: 96% F: 28% Cl_{sys}: 2000 mL/min E: ≈1	Frequent: hepatocellular injury, hyperbilirubinaemia [22]	Myelosuppression, mucositis, alopecia, nausea and vomiting, diarrhoea, elevated liver enzyme levels, cardiotoxicity[23,24]	Studies: kinetics of idarubicin are not changed in patients with metastases[133,134] Recommendation: 50% dose reduction if serum bilirubin level 20–34 μmol/L. Contraindicated if serum bilirubin level >34 μmol/L[22]
Imatinib	3	Metabolism: N-demethylation (CYP3A), BE 20%[22] Q_0: 0.95 V_d: 4.9 L/kg $t_{1/2}$: 18h PB: 95% E: 98%	Sporadic: hyperbilirubinaemia, hepatocellular injury[22]	Myelosuppression, oedema, myalgia, fatigue[22]	Recommendations: stop treatment if serum bilirubin level >3 × ULN or transaminase levels >5 × ULN[22]

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Table IV. Contd

Drug	Cat[a]	Kinetic parameters[b,c,d]	Frequency of hepatic adverse effects[e]	Dose-dependent adverse reactions	Studies performed and dose recommendations
Irinotecan	2	Metabolism: esterases, glucuronidation, CYP3A4, BE 25%[22,65] Q_0: 0.75 V_d: 75 L/kg $t_{1/2}$: 10h PB: 65% Cl_{sys}: 430 mL/min E: 0.36		Myelosuppression, cholinergic syndrome (diarrhoea), alopecia, nausea and vomiting, mucositis, pulmonary toxicity[22,23]	Study: in patients with gastrointestinal cancer and cholestasis, the AUC for SN-38 (active metabolite) was 50% increased (serum bilirubin level 1.1–1.5 × ULN) or 100% increased (>1.5 ULN)[135] Recommendation: if serum bilirubin level >1.5 × ULN or transaminase levels >5 × ULN, dose reduction according to dose-dependent toxicity. Contraindicated if serum bilirubin level >5 × ULN.[22] Dose of irinotecan should be 350 mg/m^2 in patients with serum bilirubin level 1.1–1.5 × ULN and 200 mg/m^2 when serum bilirubin level >1.5 × ULN[135]
Mitoxantrone	1	Metabolism: mono- or dicarboxylation (inactive), BE 25%[22] Q_0: 0.95 V_d: 10–15 L/kg $t_{1/2}$: 57h PB: 76% Cl_{sys}: 750 mL/min E: 0.79	Frequent: hepatocellular injury[25]	Myelosuppression, mucositis, nausea and vomiting, diarrhoea, menstrual disorders, neurological disorders, cardiotoxicity, alopecia, hepatotoxicity, nephrotoxicity[22,24]	Studies: clearance reduced by 50% in patients with moderate liver disease[137] Patients with serum bilirubin level <60 μmol/L tolerate 14 mg/m^2, patients with serum bilirubin level >60 μmol/L and bad performance status have higher mortality with this dosage.[27] In patients with liver metastases, a half-life of mitoxantrone correlated with serum bilirubin level and cholestasis[28] Recommendation: dose adjustment (8 mg/m^2) or contraindicated (bad performance status) in patients with serum bilirubin level >60 μmol/L[27]
Paclitaxel	2	Metabolism: CYP3A, CYP2C8, BE >5%[30] Q_0: 0.95 V_d: 2.0 L/kg $t_{1/2}$: 3h PB: 95% Cl_{sys}: 380 mL/min E: 0.41	Sporadic: hepatocellular injury, cholestasis Rare: hyperbilirubinaemia, liver failure[22]	Myelosuppression, peripheral neuropathy, arthralgia, myalgia, hypotension, nausea and vomiting, diarrhoea, mucositis, cardiotoxicity (arrhythmias, bradycardia)[22,24]	Studies: liver disease/liver cirrhosis appears to be a risk factor for systemic toxicity.[31,32] Increased risk for myelosuppression in patients with increased transaminase levels and/or serum bilirubin level >25 μmol/L.[33] In patients with increased transaminase levels (3–10 × ULN) and hyperbilirubinaemia (1.3–2 × ULN), clearance was decreased by ≈40%[34] Recommendation: monitor patients with liver disease well for adverse effects. Do not administer in patients with decompensated liver disease[22,34]

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Table IV. Contd

Drug	Cat[a]	Kinetic parameters[b,c,d]	Frequency of hepatic adverse effects[e]	Dose-dependent adverse reactions	Studies performed and dose recommendations
Topotecan	2	Metabolism: esterases, BE 20%[46] Q_0: 0.6 V_d: 1.9 L/kg $t_{1/2}$: 2.4h PB: 35% F: 32% Cl_{sys}: 825 mL/min E: 0.55		Myelosuppression, nausea and vomiting, alopecia, mucositis, diarrhoea[22,23]	Studies: 14 patients with increased transaminase levels and/or hyperbilirubinaemia (some with cirrhosis) were treated with 1.5 mg/m^2. Topotecan clearance correlated with ICG clearance but no more adverse effects were observed in patients with liver disease.[47] On the other hand, two-thirds of patients with hepatocellular carcinoma treated with topotecan developed grade IV neutropenia[48] Recommendation: no dose adjustment for patients with hepatic dysfunction but monitor patients well for systemic toxicity[47]
Vinblastine	1	Metabolism: CYP3A4, BE >50%[24] Q_0: 1 V_d: 20 L/kg $t_{1/2}$: 25h PB: 75% Cl_{sys}: 865 mL/min E: 0.96		Myelosuppression, nausea and vomiting, alopecia, mucositis, neurotoxicity (peripheral and autonomic), inappropriate ADH secretion (SIADH)[22,24]	Recommendation: 50% dose reduction if serum bilirubin level >50 μmol/L[22]
Vincristine	3	Metabolism: CYP3A4, BE 70%[24] Q_0: 0.9 V_d: 8.0 L/kg $t_{1/2}$: 23h PB: 75% Cl_{sys}: 140 mL/min E: 0.14		Myelosuppression, nausea and vomiting, alopecia, mucositis, neurotoxicity (peripheral and autonomic), inappropriate ADH secretion (SIADH)[22,24]	Studies: in the presence of cholestasis/hyperbilirubinaemia half-life was prolonged.[51] In patients with leukaemia or lymphoma and cholestasis, AUC and toxicity were increased[52] Recommendation: 50% dose reduction if serum bilirubin >50 μmol/L.[22] Some authors advise 50% dose reduction also if alkaline phosphatase level is increased[26]
Vindesine	4	Metabolism: CYP3A, BE >20%[22,23] V_d: 8.8 L/kg $t_{1/2}$: 24h Cl_{sys}: 17.5 mL/min		Myelosuppression, nausea and vomiting, alopecia, mucositis, neurotoxicity (peripheral and autonomic), inappropriate ADH secretion (SIADH)[22,24]	Recommendation: monitor patients for dose-dependent adverse effects. Dose may need to be adjusted in patients with hyperbilirubinaemia (see vincristine)[22]

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Table IV. Contd

Drug	Cat[a]	Kinetic parameters[b,c,d]	Frequency of hepatic adverse effects[e]	Dose-dependent adverse reactions	Studies performed and dose recommendations
Vinorelbine	1	Metabolism: CYP 3A, BE 50%[24,53] Q_0: 0.85 V_d: 75 L/kg $t_{1/2}$: 30h PB: 15% F: ≈40%		Myelosuppression, neurotoxicity (peripheral and autonomic), mucositis, alopecia, pulmonary toxicity[22,23]	Studies: in 19 patients with liver metastases, clearance was reduced by 50% in patients with >75% of the liver replaced by tumour.[54] Recommendation: 50% dose reduction if >75% of liver replaced by tumour[54] or if serum bilirubin level >34 μmol/L[53]

a Drugs were categorised as follows: category 1: high hepatic extraction [E >60%, F <40%]; category 2: intermediate hepatic extraction (E = 30–60%, F = 40–70%); category 3: low hepatic extraction (E <30%, F >70%); category 4: hepatic extraction not known.

b The fraction metabolised or excreted by bile (1-Q_0: fraction excreted unchanged by the kidney).

c For calculation, bodyweight was assumed to be 70kg.

d Calculated as described in equation 4 of the main article.

e Frequent: >10% of patients treated; sporadic: 1–10%; rare: <1%.

ADH = antidiuretic hormone; **AUC** = area under the concentration-time curve; **Cat** = drug category; Cl_{sys} = systemic clearance; **CYP** = cytochrome P450; **E** = hepatic extraction; **EGFR** = epidermal growth factor receptor; **F** = bioavailability; **ICG** = indocyanine green; **PB** = fraction bound to proteins; Q_0 = extrarenal dose fraction; **SIADH** = syndrome of inappropriate antidiuretic hormone secretion; $t_{1/2}$ = dominant half-life; **ULN** = upper limit of normal; V_d = volume of distribution; **VOD** = veno-occlusive disease.

and kinetic data for such drugs should be available in patients when such drugs are approved.

Treatment with antineoplastic agents can either lead to liver disease or, for drugs metabolised by the liver and/or excreted by the bile, to increased systemic toxicity in patients with liver disease. For such drugs, there is an additional type of toxicity that may be relevant. In several patients with chronic hepatitis B, the immunosuppressive effect of antineoplastic agents was associated with a flare up of their hepatitis due to increased replication of the hepatitis B virus.[139-145] Since this condition is potentially fatal,[141] but can be prevented by previous treatment or prophylaxis with antiviral agents, the immune status regarding hepatitis B should be known before treatment with antineoplastic drugs.

5. Conclusion

In conclusion, there are currently considerable gaps in the data needed for safe administration of antineoplastic drugs in patients with decreased hepatic function. Drug authorities should urge pharmaceutical companies to provide data before these drugs are approved. Considering kinetics, in particular data about oral bioavailability and/or hepatic extraction should be known. For drugs with a predominant hepatic metabolism and/or excretion, the kinetics in patients with liver metastases and/or cholestasis should be known before marketing authorisation is provided.

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Correspondence and offprints: Professor *Stephan Krähenbühl*, Clinical Pharmacology & Toxicology, University Hospital, Basel, CH-4031, Switzerland.
E-mail: kraehenbuehl@uhbs.ch