University College London Hospitals NHS
NHS Foundation Trust

Dosage Adjustment for Cytotoxics in Hepatic Impairment

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This table is a guide only. Pharmacokinetic, Summary of Product Characteristics (SPC), relevant pharmaceutical company data and various references have been reviewed for each drug. From this information, a recommendation has been suggested. Input of the full clinical picture of the patient should always be taken into account. If a patient is following a specific clinical trial or protocol, it is advisable to follow the associated dose modifications.

The reference ranges for UCL Hospitals NHS Trust are as follows:

- Bilirubin: 3 - 17 μmol/L
- Alkaline phosphatase (ALP): 0 – 455 U/L
- Alanine transaminase (ALT): 8 – 63 U/L
- Aspartate transaminase (AST): 5 – 40 IU/L

Please note that reference ranges will vary from hospital to hospital and this should be taken into account when interpreting the data.

Drug	Pharmacokinetics	Available Information	Recommendation
Alemtuzumab	$t^1/_2$ 23 – 30 hours. Serum concentration rise corresponds with reduction in malignant lymphocytosis. Different pharmacokinetic properties may be related to different tumour burden and distribution. Alemtuzumab is primarily metabolised intracellularly.	**SPC (Bayer 2008)–** No studies have been conducted in patients with hepatic impairment. **Schering** – No information, but the drug is cleared intracellularly and therefore unlikely to require reduction. **BC Cancer Agency** – No information found	Clinical decision but unlikely to require a reduction.
Amsacrine	Amsacrine is extensively metabolised in the liver. The principal metabolites, via microsomal oxidation, are much more cytotoxic than the parent drug. Excretion is via the bile. >50% excreted in faeces within 2 hours; 35% in urine	**SPC (Goldshield 2005)** – for patients with impaired liver function, reduce dose by 20-30% (to 60-75mg/m2 per day). **BC Cancer Agency** – if bilirubin 26-51μmol/L, give 40% of usual dose. If bilirubin> 51 μmol/L then reduce further or omit. **AML 17** – if bilirubin >34μmol/L give 60% dose.	If bilirubin >34μmol/L give 60% dose.
Arsenic Trioxide	Arsenic is stored mainly in liver, kidney, heart, lung, hair and nails. Trivalent forms of arsenic are methylated in humans and mostly excreted in the urine.	**SPC (Cephalon 2008)** – the safety of the drug in patients with hepatic impairment has not been studied. **Johns et al**[1] – A phase I study was conducted in 23 subjects with unresectable, carcinoma with varying degrees of hepatic dysfunction. Doses were escalated from 0.25mg/kg to 0.5mg/kg and then by increments of 0.5mg/kg. The authors found the drug was well tolerated in this group of subjects.	Clinical decision – unlikely to require reduction.

Drug	Pharmacokinetics	Available Information	Recommendation
ATRA (tretinoin)	After an oral dose of radiolabelled tretinoin, about 60% of the radioactivity was excreted in urine and about 30% in faeces. The metabolites found in urine were formed by oxidation and glucuronidation.	**SPC (Roche 2008) –** Due to limited information reduce dose to 25mg/m^2 in patients with hepatic impairment. **BC cancer agency –** 25mg/m^2 is recommended in patients with hepatic impairment as no studies have been done.	Dose at 25mg/m^2
Azacitadine	Azacitadine undergoes rapid elimination. The route of elimination requires further study but the drug appears to undergo hepatic metabolism with excretion. Excretion of unchanged drug and metabolites is via the kidneys. The activity of metabolites is unknown.	**Pharmion** – In the 3 NCI studies involving azacitadine there was no significant increase in adverse reactions in patients with hepatic impairment compared with those with normal hepatic function. However the drug should be used with caution as it is metabolised by hepatic enzymes. In addition there is also some limited data suggesting that azacitadine may be hepatotoxic in patients with severe pre existing hepatic impairment. The starting dose for the drug is 75mg/m^2 SC for 7 days this is regardless of hepatic function and no dose adjustments should be made. The dose is titrated up to 100mg/m^2 if no toxicity occurs and benefit has not been seen with the starting dose.	No dose reduction required for starting dose of 75mg/m^2. Clinical decision as to whether the dose is increased to 100mg/m^2.
Bevacizumab	Terminal half-life 19-20 days. Male patients and those with a higher tumour burden have a greater clearance than female patients. The drug does not rely primarily on elimination through kidneys or liver.	**SPC (Roche 2008)** – The safety and efficacy have not been studied in this group of patients. **Roche** – Decision on whether to use should be based on risk versus benefit. **ICON 7** – Current trial studying bevacizumab in ovarian cancer excludes patients with bilirubin >1.5XULN and serum transaminases 2.5XULN.	Clinical decision.
Bexarotene	Metabolised by oxidation via CYP450 3A4 and glucuronidation. Less than 1% excreted in the urine.	**SPC (Cephalon 2007) –** Contraindicated in hepatic insufficiency.	Likely to require reduction – clinical decision on whether to use.
Bleomycin	t½ 2-4 hours. Rapid distribution to body tissues (highest concentration in skin, lungs, peritoneum & lymph). Inactivation takes place primarily in the liver. ~ 2/3 of drug are excreted unchanged in the urine, probably by glomerular filtration.	**SPC (Kyowa Hakko 2006)** – No information. **Kyowa Hakko** – Patients with abnormal liver function tend to develop lung dysfunction. **BC Cancer Agency** – No adjustment required.	Clinical decision.
Bortezomib	Metabolised by oxidation via CYP450 3A4 and 2C9. Small amount excreted in the urine.	**SPC (Janssen Cilag 2008) –** Not studied in hepatic impairment. Significant impairment may have an impact on clearance. Patients with hepatic dysfunction should be treated with extreme caution and a dose reduction should be considered. Contraindicated in severe impairment**.** **Ortho Biotech** – As SPC **BC cancer agency –** Use with caution	Use with caution in mild to moderate hepatic impairment, likely to require reduction. Contraindicated in severe impairment.

Drug	Pharmacokinetics	Available Information	Recommendation
Busulfan	The mean elimination t½ is 2.57hrs. Extensive hepatic metabolism to at least 12 metabolites. After low and high doses, 1 & 2% respectively of unchanged drug is excreted in the urine. The majority of an oral dose is excreted in the urine as methanesulfonic acid, an inactive metabolite.	**SPC (Pierre Fabre 2008) -** The drug has not been studied in patients with hepatic impairment therefore advises to use with caution in severe hepatic impairment. **GSK** – no information. **BC cancer agency** – no information	Consider dose reduction in patients with raised liver enzymes.
Capecitabine	Extensive absorption (~70%) after food intake. Metabolism is first in the liver and then in the tumour. Up to 96% dose is recovered in the urine. Terminal t½ = 0.75 hours.	**SPC (Roche 2009)** – insufficient safety and efficacy data are available in patients with hepatic impairment to provide dose adjustment recommendation. No information is available on hepatic impairment due to cirrhosis or hepatitis. **Twelves et al**[2] have evaluated the use of capecitabine in patients with mild to moderate hepatic dysfunction caused by liver metastases. No significant differences in the pharmacokinetic parameters of the main metabolites were seen in this group compared with patients with normal function indicating there is no need for prior adjustment of the dose in this patient population. **BC Cancer Agency** – no dose adjustment required in mild to moderate hepatic impairment if due to liver metastases. Drug has not been studied in severe hepatic impairment.	Lack of information available. In patients with mild to moderate hepatic dysfunction due to liver metastases, 100% dose probably ok.
Carboplatin	Excretion is primarily by glomerular filtration in urine, with most of the drug excreted in the first 6hrs. ~32% dose is excreted unchanged. Terminal t½ ~ 6 days.	**SPC (Hospira 2006**) – no information. Transient increases in liver enzymes have been reported. ALP was increased in 30% patients, AST increased in 15% patients, and bilirubin in 4% patients. **Mayne Pharma** – no further information. **BC Cancer Agency** – no adjustment required.	Probably no dose reduction necessary.
Carmustine	Partially metabolised to active species by liver microsomal enzymes, which have a long t½. It is thought that the antineoplastic activity may be due to metabolites. ~60-70% of the total dose is excreted in the urine in 96hrs and ~10% as respiratory CO_2. Terminal t½ ~ 1 hour.	**SPC (Bristol Myers Pharmaceuticals 2007)** – when high doses have been used, a reversible type of hepatic toxicity, manifested by increased transaminases, ALP and bilirubin levels, has been reported in a small percentage of patients. **BMS** – very little information. **BC Cancer Agency** – No guidelines available. Dosage adjustment may be necessary	Clinical decision.

Drug	Pharmacokinetics	Available Information	Recommendation
Cetuximab	Elimination is via binding EGFRs in a large number of tissues. Half life =3-7 days.	**SPC (Merck Sorono 2008) –** Only patients with adequate hepatic impairment have been studied to date i.e. those with serum transaminases <5 x ULN and bilirubin <1.5 x ULN. Pharmacokinetic data suggests that hepatic status does not affect the pharmacokinetic characteristics of cetuximab.	Unlikely to require a reduction.
Chlorambucil	Good oral absorption - absorption slowed and decreased by 10-20% if ingested with food. Metabolism is predominantly in the liver via hepatic microsomal enzyme oxidation system. <1% excreted unchanged in the urine. t½ = 2 hours.	**SPC (GSK 2007)** – Consider dose reduction in patients with gross hepatic dysfunction. **BC Cancer Agency** – Dose adjustments should be considered but no recommendations. **GSK –** – Experiments in mice have lead to the hypothesis that hepatic cytochrome P-450 is involved in the metabolism. The drug has been administered to patients with hepatic impairment in the treatment of primary biliary cirrhosis. There are no absolute recommendations on the necessity of a dose reduction. Given the pharmacokinetics of the drug it is advised to reduce the dose in severe hepatic impairment then titrate upwards according to response.	Dose reduce in patients with gross hepatic dysfunction. Modify dose according to response. Once the tolerance is established after the first month of therapy the dosage should be modified according to response e.g. level of haematological suppression.
Chlormethine (Mustine)	Following intravenous injection, it is rapidly converted to a reactive ethyleneimmonium ion. Usually disappears from the blood within approximately ten minutes. $t^1/_2 = 15$ minutes. Less than 0.01% of the drug is excreted unchanged in the urine. 50% is excreted in the urine as metabolites after 24 hours.	**SPC** - no information available	No information available. Probably no dose reduction necessary. Clinical decision
Cisplatin	Non-enzymatically transformed into multiple metabolites. There is good uptake of cisplatin in the kidneys, liver and intestine. Distributes into third spaces such as ascites and pleural fluid. The elimination of intact drug and metabolites is via the urine. In the first 24hrs 20-80% is excreted.	**SPC (Pharmacia 2008)** – no information. **Mayne Pharma** – no information **BC Cancer Agency** – no adjustments required	No dose reduction necessary.
Cladribine	Pro-drug - activated by intracellular phosphorylation. The nucleotide that is formed accumulates in the cell and is incorporated into the DNA. ~20% was recovered unchanged in the urine.	**SPC (Lipomed GmbH 2008)** – There is inadequate data on dosing of patients with hepatic insufficiency. Contraindicated in moderate or severe hepatic impairment. **Janssen-Cilag** – The role of the liver in cladribine clearance has not been determined. In a pharmacokinetic study, it was found that the lowest cladribine clearance was in one patient with a bilirubin of 39μmol/L.	Lack of information available. Clinical decision.

Drug	Pharmacokinetics	Available Information	Recommendation
Clofarabine	Eliminated by a combination of renal and non-renal excretion. After 24 hours 60% of the dose is excreted unchanged in the urine. Non renal routes of elimination are currently unknown.	**SPC (Genzyme Therapeutics 2008) –** No experience in patients with hepatic impairment. Contraindicated in severe hepatic impairment and should be used with caution in mild to moderate impairment**.** Severe being defined as bilirubin>1.5xULN, ALT>5xULN **Bioenvision** – as above.	Use with caution in mild/moderate impairment. Contraindicated in severe hepatic impairment.
Crisantaspase	Plasma t½ is 7-13 hours.	**SPC (OPi 2005) -** no information **Opi –** As a general rule the product should not be used in severe hepatic impairment. In cases of hepatic failure the company cannot recommend its use unless the clinician deems it a risk versus benefit case. **UKALL2003 –** no dose modifications recommended	Clinical decision
Cyclophosphamide	Pro-drug – converted by hepatic microsomal enzymes to alkylating metabolites (great interpatient variability in metabolism). Excretion primarily renal. 30% is excreted as unchanged drug. t½ is 4-10 hours in adults and 1- 6.5 hours in children.	**SPC (Pharmacia 2007) -** not recommended in patients with a bilirubin >17μmol/L or serum transaminases or ALP more than 2-3 x upper limit of normal. In all such cases doses should be reduced. **Asta Medical** – In patients with severely impaired hepatic function, there is a decrease in the peak plasma alkylating activity but the overall t½ is significantly increased and the total exposure to alkylating metabolites is the same as in patients with normal hepatic function. It has been reported that disorders of liver function without signs of jaundice may not be a contraindication and that dosage adjustment may not be necessary. **BC Cancer Agency** – no adjustments required	Consider SPC recommendations; however, exposure to active metabolites may not be increased, suggesting that dose reduction may not be necessary. Clinical decision.
Cytarabine	Cytarabine is concentrated in the liver. A major fraction of a dose is inactivated by cytidine deaminase in the liver and other body tissues. After 24hrs, 80% dose has been eliminated either as the inactive metabolite or as unchanged cytarabine, mostly in urine but some in bile.	**SPC (Pharmacia 2008)** – the human liver apparently detoxifies a substantial fraction of the administered dose. The drug should be used with caution and at a reduced dose when liver function is poor. **Faulding** – Limited guidance indicates that the drug should be started at 50% of the regular dose in those patients with severe hepatic dysfunction (bilirubin >34umol/L). Subsequent doses can be escalated in the absence of toxicity. The hepatotoxic properties of the drug have not been proven. **Pfizer** – No further information. **BC Cancer agency** – As above	If bilirubin >34umol/L, give 50% dose. Escalate doses in subsequent cycles in the absence of toxicity.
Dacarbazine	Dacarbazine (DTIC) is assumed to be inactive. Microsomal metabolism in the liver produces one main metabolite; AIC. ~50% DTIC is renally cleared. ½ of this is unchanged DTIC & ~ ½ is AIC. DTIC is renally tubularly secreted, rather than glomerularly filtered.	**SPC (Medac GmbH 2008)** – If mild to moderate hepatic insufficiency alone dose reductions are not required. In patients with combined renal and hepatic impairment, elimination of dacarbazine is prolonged. No validated recommendations on dose reductions can be given currently. **Bayer** – No further information. **BC Cancer Agency** – Adjustment required, alternatively monitor for toxicity.	Activated and metabolised in the liver. Can be hepatotoxic. Consider dose reduction.

Drug	Pharmacokinetics	Available Information	Recommendation
Dactinomycin	15% eliminated by hepatic metabolism ~30% of the dose was recovered in the urine and faeces in 1week. The terminal plasma t½ ~ 36hrs.	**SPC (MSD 2006) -** No recommendations. **MSD** – Some correspondence of children with Wilms tumour and hepatotoxicity[3]. Because of the sensitivity to chemotherapy of Wilms' tumour, lower doses may be appropriate (0.5 – 1mg/m^2). Case reports of veno-occlusive disease have been reported when patients have administered the drug in a multidrug regimen. No information on dose reductions. **BC Cancer Agency** – t½ is prolonged in patients with hepatic dysfunction, adjustments required but no guidelines.	Consider dose reduction in severe hepatic disease.
Dasatinib	Extensively metabolised in humans by many enzymes. Dasatinib is a substrate and inhibitor of CYP3A4. Mainly excreted in the faeces and 4% in the urine.	**SPC (BMS 2008)** – No clinical trials were conducted in patients with decreased liver function. Exposure to dasatinib is thought to increase with impaired liver function. The drug should be used with caution in moderate to severe impairment. **BMS-** as above plus data that was presented to the FDA demonstrates that elevations in LFTs did occur when on treatment	Use with caution in severe hepatic impairment.
Daunorubicin	Daunorubicin is rapidly taken up by the tissues, especially by the kidneys, liver, spleen and heart. Subsequent release from of drug and metabolites is slow (t½ ~ 55hrs). Rapidly metabolised in the liver & the major metabolite, daunorubicinol is also active. It is excreted slowly in the urine, mainly as metabolites with 25% excreted within 5 days. Biliary excretion accounts for 40% elimination.	**SPC (Winthrop pharmaceuticals 2008)** – A dose reduction is recommended in patients with impaired hepatic function. See recommendations. **Aventis** – As SPC **UKALL 2003** – Check LFTs only if patient jaundiced. Do not alter dose for abnormal transaminases. **BC Cancer Agency** – as guidelines however recommends not to give if bilirubin >85µmol/L	**Bilirubin µmol/L** — **Dose** <20 — 100% 20-50 — 75% >50 — 50%
Docetaxel	Cytochrome P450 mediated metabolism. In animal studies distributed to all tissues and organs except the brain. 6% and 75% of the dose is excreted via the renal and faecal route respectively within 7 days. Terminal t½ = 2.5 hours.	**SPC (Sanofi-Aventis 2008)** – If ALT +/or AST > 1.5xULN and ALP >2.5xULN – give 75mg/m2 If Bilirubin >22µmol/L +/or ALT/AST >3.5ULN with ALP >6xULN, docetaxel should not be used unless strictly indicated.	As per SPC
Doxorubicin	Mainly metabolised in the liver by cytochrome P450. Rapidly cleared from plasma and slowly excreted in the urine and bile (50% of drug recoverable in the bile or faeces in 7 days).	**SPC (Pfizer 2006)** – for bilirubin 20 - 51µmol/L, give 50% dose. For bilirubin >51µmol/L, give 25% dose. **Koren et al**[4], suggest the above and if bilirubin >85µmol/L, give 0% dose. If AST 2-3 x normal, give 75% dose. **UKALL 2003** – Check LF Ts only if patient jaundiced. Do not alter dose for abnormal transaminases. **BC Cancer Agency**- As recommendations**.**	**Bilirubin /µmol/L** — **Dose** 20-51 — 50% 51-85 — 25% >85 — omit If AST 2-3 x normal, give 75% dose. If AST >3x ULN, give 50% dose

Drug	Pharmacokinetics	Available Information	Recommendation
Epirubicin	Mainly metabolised in the liver. Slow elimination through the liver is due to extensive tissue distribution. 27-40% biliary excretion. Urinary excretion accounts for ~10% of dose in 48hrs.	**SPC (Hospira 2006)** – for bilirubin 24 - 51µmol/L, give 50% dose, for bilirubin >51µmol/L, give 25% dose. **BC Cancer Agency:** If AST 2-4 x ULN or bili 21-51µmol/L give 50% dose , if AST >4 x ULN or bili >51 µmol/L then give 25% dose	**Bilirubin /µmol/L** — **Dose** 24-51 — 50% 51-85 — 25% >85 — omit
Estramustine	Dephosphorylated in the intestines then oxidised in the liver. 14-21% excreted in the faeces and 22-36% in the urine.	**SPC (Pharmacia 2008) –** Use with caution in hepatic impairment **BC Cancer Agency –A**dminister with caution but no recommendations.	Pharmacokinetics indicate that dose should be reduced in hepatic impairment. Clinical decision
Etoposide	Liver metabolised, yielding inactive metabolites. ~45% of an administered dose is excreted in the urine, 29% being excreted unchanged in 72 hrs.	**SPC (BMS 2007)** – Etoposide reaches high concentrations in the liver and kidney. Etoposide use is contra-indicated in patients with severe hepatic dysfunction. **BMS** – Creatinine clearance is the strongest predictor of etoposide clearance. There is conflicting information. Some studies indicate that toxicity, clearance and t½ are not altered in impaired hepatic function. **Koren et al**[4] suggest the following: Bilirubin: 26-51µmol/L or AST: 60-180 units/L -50% dose Bilirubin: >51µmol/L or AST: >180 units/L - omit dose **BC Cancer Agency** – Bilirubin 25-50µmol/L: 50% dose, 50-85µmol/L: 25% dose, >85 µmol/L – do not administer. Minor alterations in liver function e.g. transaminase elevations do not require dose reduction if renal function is normal.	Arguments for and against dose reduction. Bilirubin 26-51 or AST 60-180 – give 50% dose Bilirubin >51 or AST >180 – clinical decision.
Fludarabine	Rapidly dephosphorylated in plasma to 2-F-ara-ATP, which is necessary for cellular uptake. ~60% of an administered dose is excreted in the urine within 24hrs.	**SPC (Bayer 2008)** – No information in this group of patients therefore use with caution. **Schering** – Fludarabine is mainly eliminated by the renal route, therefore dose reductions are not necessary. However, there have been reports of liver dysfunction (<1 in 1000) – mainly raised LFTs. Use with extreme caution. **BC Cancer Agency**- use with caution if benefit outweighs risk.	No dose changes recommended

Drug	Pharmacokinetics	Available Information	Recommendation
Fluorouracil	Fluorouracil is distributed through the body water. Activated in target cells, catabolized in the liver - most of dose (80%) eliminated by liver. 60-80% is excreted as respiratory CO_2 , 2-3% by biliary system. Following a single IV dose, ~15% dose is excreted unchanged in the urine. t½ ~ 10 minutes.	**SPC (medac GmbH 2007)** – Dose reduction is advisable in impaired hepatic function. **Faulding** – Although ~50% of fluorouracil is metabolised by the hepatic route, the clinical significance is unclear. Some studies of plasma and tissue concentration of the drug and derivatives in patients with hepatocellular carcinoma and liver cirrhosis or liver metastases detected no change in drug disposition relating to liver dysfunction, indicating no dose reduction is required. However, a dose reduction of the initial dose is advised of 1/3 to 1/2 in hepatic impairment. **Koren et al**[4] suggest a 50% dose reduction, then increase if no toxicity. **BC Cancer Agency** – Bilirubin above 86 µmol/L – omit dose	**Bilirubin /µmol/L** / **AST** / **Dose** <85 / <180 / 100% >85 or >180 / CI Clinical decision. Moderate hepatic impairment; reduce initial dose by 1/3. Severe hepatic impairment, reduce initial dose by 1/2. Increase dose if no toxicity
Gemcitabine	Rapid metabolism by cytidine deaminase in the liver, kidney, blood and other tissues. The active intracellular metabolites have not been detected in plasma or urine. Urinary excretion of parent drug and inactive metabolite (dFdU) accounts for 99%. Terminal t½ is ~1 hour – this increases if the drug is administered over a longer period.	**SPC (Lilly 2007)** – use with caution in patients with hepatic insufficiency. **Lilly** – Very limited information available. Egorin et al looked at 8 patients with AST >2xULN and 19 patients with bilirubin (28 – 196µmol/L) No dose limiting toxicities were observed in patients with AST elevations. Half of the patients in the raised bilirubin group developed dose limiting toxicities. **BC Cancer Agency** - Use a lower starting dose of 800 mg/m^2 with total bilirubin > 27 µmol/L.[5]	AST elevations do not seem to cause dose limiting toxicities.. If bilirubin > 27 µmol/L, initiate treatment with dose of 800 mg/m^2.
Gemtuzumab	The elimination of gemtuzumab ozogamicin is hypothesised to be principally via internalisation and subsequent intracellular breakdown. First, after binding to the CD33 antigen, gemtuzumab ozogamicin is eliminated in the plasma by internalisation into the cells. Secondly, results from animal studies suggest that the hepatic excretory/metabolism route and gastrointestinal secretion is probably the major elimination pathway, however, renal elimination was seen to a smaller extent. At this time the exact elimination pathway in humans has yet to be described.	**Wyeth –** Proposed major pathways involved in the elimination of gemtuzumab ozogamicin are via internalization and intracellular breakdown after binding to the CD33 antigen and hepatic metabolism. Use with caution in patients with hepatic impairment as they are more likely to suffer from veno-occlusive disorder. The drug has not been studied in patients with a bilirubin >34 µmol/L.	Use with caution – may increase the risk of veno-occlusive disease.

Drug	Pharmacokinetics	Available Information	Recommendation
Hydroxycarbamide (Hydroxyurea)	After oral administration, hydroxyurea is readily absorbed from the GI tract. 50% hepatically metabolised. Peak plasma concentrations are reached by 2hrs. 50% of dose recovered in urine within 12 hours, mainly as intact drug. The rest is excreted as carbon dioxide via the lungs or via the urine as urea. t½ = 2-4 hours.	**SPC (medac GmbH 2006)** – no information in this group of patients therefore use with caution. **BMS** – no information. **BC Cancer Agency** – monitor haematological parameters	Lack of information available. Probably no dose reduction necessary Clinical decision. Monitor patient
Idarubicin	Oral idarubicin has rapid but erratic absorption, about 30% bioavailability. Extensive liver metabolism to idarubicinol which has equipotent activity and a much longer t½ than idarubicin (50 vs 18hrs). Elimination is via the hepatobiliary and renal system, mostly as idarubicinol. 17% (IV) / 8% (oral) is recovered in the faeces over 5 days and 16% (IV) / 5% (oral) is recovered in the urine over 4 days.	**SPC (Pharmacia 2008)** – in a number of Phase III clinical trials, treatment was not given if bilirubin >34µmol/L. For other anthracyclines, 50% dose reduction if bilirubin in range 21-34µmol/L. Contra-indicated in severe liver impairment. **Pfizer –** no further information **Cancer Chemotherapy Handbook** - If bilirubin >85µmol/L, then the drug should not be administered[6]. **Zanette et al** – no changes in idarubicin pharmacokinetics were seen in patients with abnormal LFT's (Bilirubin 1.5-2x ULN and ALP 1- 4x ULN) but it 'cannot be excluded that the clearance of the drug and its metabolite may be affected in patients with severe hepatic dysfunction[7]. **BC Cancer Agency** – if bilirubin 40-85 µmol/L, then give 50% dose reduction. If bilirubin >85µmol/L, then CI.	**Bilirubin /µmol/L** — **Dose** <40 — 100% 40-85 — 50% >85 — omit
Ifosfamide	Pro-drug – converted by hepatic microsomal enzymes to alkylating metabolites. Excretion primarily renal. ~80% dose excreted as parent compound. Serum t½ ranges between 4-8hrs.	**SPC (Baxter 2007)** – contra-indicated in patients with a bilirubin >17µmol/L or serum transaminases or ALP more than 2.5 x upper normal limit. **Asta Medical** – Good liver function is important for both activation and elimination of ifosfamide. Ifosfamide is itself not hepatotoxic, however, concomitant hepatotoxic drug administration should be avoided.	As per SPC recommendations. Clinical decision.
Imatinib	High oral bioavailability (98%). Main circulating metabolite is N-demethylated piperazine derivative. Catalysed by cytochrome P450 CYP3A4. Mainly hepatic metabolism, 68% excreted in faeces and 13% in urine in 7 days. t½ = 18 hours.	**SPC (Novartis 2008) –**If bilirubin >3xULN or liver transaminases >5X ULN withhold imatinib until bilirubin < 1.5 x ULN or liver transaminases < 2.5 x ULN. Treatment can be continued at a reduced dose – In adults- 400 mg od → 300 mg od; 600 mg od → 400 mg od, 800 mg od → 600 mg od. In children from 340 to 260mg/m2/day. Patients with mild/moderate/severe impairment should be given the minimum recommended dose of 400mg/day and this should be reduced if it is not tolerated. **BC Cancer Agency** – as SPC	Dose as SPC

Drug	Pharmacokinetics	Available Information	Recommendation
Irinotecan	Metabolism is primarily hepatic, where irinotecan is rapidly converted to active metabolite SN-38 by hepatic carboxylesterase enzymes. Excretion is predominantly biliary – 64% excreted in faeces. The mean 24hr urinary excretion of irinotecan and SN-38 (its active metabolite) was 19.9% and 0.25% respectively.	**SPC (Pfizer 2008)** – In patients with a bilirubin <1.5xULN, give 350mg/m^2. Patients with a bilirubin 1.5–3xULN give 200mg/m^2. Patients with a bilirubin beyond 3xULN should not be treated with irinotecan. No data is available in patients with hepatic impairment that are treated with a irinotecan combination regimen. **Aventis** - treatment of patients with initial total bilirubin levels > 3xULN with a starting dose of 100mg/m^2 is currently under investigatiom. **Pfizer-** if using a weekly regimen maximum tolerated dose if bilirubin 1.5-3xULN, ALT >5xULN is 60mg/m2, if bilirubin 3.1-5xULN, ALT <5xULN is 50mg/m2, if bilirubin <1.5 x ULN, ALT is 5-20 x ULN is 60mg/m2, if bilirubin 1.5-5 x ULN, ALT is 5-20 x ULN is 40mg/m2. **BC Cancer Agency** – If using a 3 or 4 weekly cycle then consider a dose reduction if the bilirubin is between 17-35µmol/L and the patient has a combined history of pelvic/abdominal radiation. If using a 6 weekly cycle then consider starting the dose at 100mg/m2 if the bilirubin is between 17-35µmol/L and the patient has a combined history of pelvic/abdominal radiation.	**Bilirubin /µmol/L** — **Dose/mg/m^2** <26 — 350 26 - 51 — 200 >51 — clinical decision
Lenalidomide	Substantially excreted via kidneys	**Celgene –** No information regarding safety in this group of patients. Thus far trials involving lenalidomide have excluded patients with hepatic impairment.	Clinical decision
Liposomal Daunorubicin	Pharmacokinetic profile significantly different to daunorubicin, with a longer t½ and a 200-400 fold reduction in volume of distribution. Metabolism appeared not to be significant at lower doses. Clearance of the liposomes may be mediated by the reticuloendothelial cells with a selective enhancement of uptake in tumour cells. Anthracyclines are excreted mostly through bile.	**SPC** – no information. **Gilead Sciences** from American prescribing information – see recommendations. Suggest extra caution and do not exceed 100mg/m2. Monitor toxicities in particular cardiotoxicity.	**Bilirubin /µmol/L** — **Dose** 20 – 50 — 75% >51 — 50% Use with caution – do not exceed 100mg/m2

Drug	Pharmacokinetics	Available Information	Recommendation
Liposomal Doxorubicin	The plasma levels are 10-20-fold higher than equivalent doxorubicin doses. There is a preferential retention of the drug in the reticuloendothelial system, such as liver, spleen and lungs. It appears that the liposomal preparation serves as a slow-release preparation for free doxorubicin.	**SPC (Schering Plough 2008)** – Liposomal doxorubicin pharmacokinetics determined in a small number of patients with elevated total bilirubin levels do not differ from patients with normal total bilirubin levels. However dose reductions are recommended in this group of patients based on breast and ovarian clinical trials. Dose reductions are as recommendations. If the patient tolerates the first dose without an increase in bilirubin or liver enzymes then the next dose can be increased by 25% and the dose can be titrated to the full dose on subsequent cycles. The drug can be administered to patients with bilirubin/liver enzymes up to 4 times the ULN. **BC Cancer Agency** – as recommendations, in addition patients with Kaposi sarcoma; bilirubin 21-51μmol/L – reduce dose by 50%, >51μmol/L then reduce dose by 75%. Do not escalate dose in this group of patients.	**Bilirubin /μmol/L** — **Dose** 20-51 — 75% >51 — 50%
Lomustine	Relatively rapid and complete oral absorption, followed by first pass metabolism. Part of lomustine metabolism is mediated through hepatic microsomal enzymes. Metabolites predominantly excreted by kidneys; 10% excreted as CO_2 and <5% in faeces.	**SPC (Medac GmbH 2007)** – liver function should be assessed periodically. **BC Cancer Agency** – Hold Lomustine if AST>5xULN and bilirubin is >25 μmol/L until liver function returns to normal.	Lack of available information. Consider dose reduction
Melphalan	Incomplete and variable oral absorption - 25-89% post oral dose; AUC decreased by 39% when taken with food. Spontaneous degradation rather than enzymatic metabolism. Percentage of dose excreted in the urine as active or toxic moiety ranges from 11-93%. 20-50% excreted in the faeces within 6 days. t½ ~ 1.5-2hrs.	**SPC (GSK 2007)** – no information. **BC Cancer Agency** – no adjustments required.	No dose changes recommended. If excessive toxicity, consider dose reduction on subsequent cycles.

Drug	Pharmacokinetics	Available Information	Recommendation
Mercaptopurine	Absorption of an oral dose is incomplete, averaging ~50%. This is largely due to first pass metabolism in the liver (less when given with food). There is enormous inter-individual variability in absorption, which can result in a 5-fold variation in AUC. It is extensively metabolised (by intracellular activation). At conventional doses clearance is primarily hepatic. Renal clearance may become important at high doses. t½ = 1-3 hrs (PO) and 0.3-1 hr (IV).	**SPC (GSK 2007)** – Mercaptopurine is hepatotoxic and liver function tests should be monitored weekly during treatment. More frequent monitoring may be advisable in those with pre-existing liver disease or receiving other potentially hepatotoxic therapy. Consider decreased dose in impaired hepatic function **UKALL 2003 guidelines** – Check LFT's only if patient jaundiced, if bilirubin >50μmol/L omit mercaptopurine until it is less than 20μmol/L and then restart at half of the previously attained dose. Escalate from 50% to 75% to 100% dose at 10-day intervals provided hyperbilirubinaemia does not recur. Do not modify dosage for elevated aminotransferases. **BC Cancer Agency –** dosage adjustment recommended but no details.	Modification based on bilirubin level (not AST/ALT) – see UKALL 2003 guidelines under available information.
Methotrexate	The dose is well absorbed at doses < 30mg/m2 – bioavailability is decreased by food and milk. Metabolism is via liver and intracellular metabolism to polyglutamated products. The drug is excreted primarily by the kidneys (>90%), although small amounts via the bile. Clearance is higher in children than in adults. t½ ~ 8 hrs.	**SPC (Hospira 2009)** – Contra-indicated in significantly impaired hepatic function. **Mayne** – see recommendations. **Koren et al**[4], Although eliminated mainly by the kidney, methotrexate should be used with caution in patients with liver dysfunction because of its hepatotoxic potential, which may lead to fibrosis and cirrhosis. The clearance rate is not likely to alter in patients with liver dysfunction who have normal renal function. Conversely, liver disease often is associated with decreased protein-binding of drugs and, therefore may theoretically lead to increased toxicity of methotrexate. **UKALL 2003 guidelines** – Check LFT's only if patient jaundiced, if bilirubin >50μmol/L omit methotrexate until it is less than 20μmol/L and then restart at half of the previously attained dose. Escalate from 50% to 75% to 100% dose at 10-day intervals provided hyperbilirubinaemia does not recur. Do not modify dosage for elevated aminotransferases. **BC Cancer agency** – as recommendations.	**Bilirubin /μmol/L** / **AST** / **Dose** <50 / And <180 / 100% 51-85 / Or >180 / 75% >85 / / CI It is expected that patients receiving high dose methotrexate will develop hypertransaminasemia and occasionally hyperbilirubinemia. These elevations can last up to 2 weeks following the methotrexate infusion and are not considered toxicity requiring discontinuation of repeated administration of methotrexate. Persistant hyperbilirubinemia and/or grade 3-4 hypertransaminasemia for longer than 3 weeks should result in discontinuation of the drug. Dose reduce, particularly in patients with concomitantly impaired renal function. Severe hepatic impairment – CI

Drug	Pharmacokinetics	Available Information	Recommendation
Mitomycin C	Pro-drug activated *in vivo.* Metabolism is predominantly in the liver. The rate of clearance is inversely proportional to the maximal serum concentration due to saturation of the degradative pathways. ~10% is excreted unchanged in the urine. Since metabolic pathways are saturated at low doses, the % dose excreted in the urine increases with increasing dose.	**SPC (Kyowa Hakko 2007)** –.No information. **Faulding** – Following metabolism at numerous sites, mitomycin is excreted in the urine and bile. Although sources have suggested that elevated AST levels may produce a prolonged plasma t½, dosage adjustment may not be necessary. **BC Cancer Agency**: No information found.	Dose reductions probably not necessary – clinical decision when AST levels > 2 x ULN.
Mitotane	Metabolised by both liver and kidneys. 60% excreted unchanged in faeces. Small proportion in bile as metabolites. 10-25% excreted in the urine as metabolites.	**SPC (HRA pharma 2008) –** Since mitotane is metabolised through the liver, plasma levels of the drug are thought to increase if the liver function is impaired. There is no experience in using the drug in patients with liver impairment and therefore data is insufficient to give dose recommendations in this group. The drug is not recommended to be used in severe hepatic impairment and it should be used with caution in those that have mild to moderate impairment. **BC cancer agency –** adjustments required but no details found**.**	Use with caution in mild/moderate impairment and avoid in severe.
Mitoxantrone	Extensive metabolism in the liver. Excretion is predominantly via the bile and faeces. 5-10% of dose is excreted in the urine within 5 days.	**SPC (Wyeth 2008)** - Careful supervision is recommended when treating patients with severe hepatic insufficiency. **Wyeth** – t½ is significantly longer in patients with abnormal LFT's (increased from 38 to 70hrs). A dose of 12mg/m^2 in hepatocellular carcinoma has a manageable toxicity. In some breast cancer trials, if bilirubin >50µmol/L, then give 50% dose. Chlebowski[8] used a dose of 14mg/m2 in breast cancer patients with hepatic dysfunction, but haematological toxicity was more severe. Patients with bilirubin 22-59µmol/L tolerate full dose, especially if they have good performance status (PS). Patients with bilirubin >60µmol/L and good PS tolerate 8mg/m2. Bilirubin >60µmol/L and poor PS, not advised.	Recommendations are based on breast cancer patients with single agent (14mg/m^2) Clinical decision depending on bilirubin level and PS. As a guide: Bilirubin <59µmol/L & good PS – 100% dose (i.e. 14mg/m^2). Bilirubin >60µmol/L & good PS – max 8mg/m2 (i.e. 40% dose reduction) Bilirubin >60µmol/L & poor PS – not recommended.

Drug	Pharmacokinetics	Available Information	Recommendation
Oxaliplatin	In vitro, there is no evidence of cytochrome P450 metabolism. Extensive nonenyzmatic biotransformation occurs. Platinum is excreted mainly by renal excretion and tissue distribution, while platinum metabolites are mainly by renal excretion. By day 5, ~54% of the total dose was recovered in the urine and <3% in the faeces.	**SPC (Sanofi-aventis 2007**)– In a phase I study including patients with several levels of hepatic impairment, frequency and severity of hepato-biliary disorders appeared to be related to progressive disease and impaired liver function tests at baseline. No specific dose adjustment for patients with abnormal LFTs was performed during clinical development. **BC Cancer Agency** – No dose adjustments required for mild to moderate impairment. No information found on severe.	Little information available. Probably no dose reduction necessary Clinical decision
Paclitaxel	Hepatic metabolism and biliary clearance is the principal mechanism for disposition. Mean values for cumulative urinary recovery of unchanged drug ranged from 1.3 to 12.6% of the dose, indicating extensive non-renal clearance.	**SPC (medac GmbH 2008)** – Patients with hepatic impairment may be at increased risk of toxicity, particularly grade III-IV myelosuppression. No evidence that toxicity increased when given as a 3-hour infusion to patients with mildly abnormal liver function. No data available in severe baseline cholestasis. When paclitaxel is given as a longer infusion, increased myelosuppression may be seen in patients with moderate to severe hepatic impairment. Paclitaxel is not recommended in patients with severely impaired hepatic function. **SPC (Abraxis 2009)** - Patients with severe hepatic impairment (bilirubin > 5 x ULN or AST/ALT > 10 x ULN) should not be treated with Paclitaxel. **BMS** – clearance, in particular, metabolite clearance, was reduced in patients with impaired liver function. This effect was positively correlated with bilirubin, transaminase and ALP levels. When liver function improves during treatment, paclitaxel and metabolite levels normalise. If bilirubin <1.25 normal value and transaminase levels < 10x normal value, a dose of 175mg/m^2 seems safe, although more haematological toxicity is seen. **Venook et al**[9] - See recommendations. Ambiguous information, if bilirubin < 26 µmol/L assume that up to 17µmol/L is normal and dose as normal. **BC Cancer Agency**- If bilirubin 1.26-2xULN give 135mg/m2, if 2-5xULN 90mg/m2 and if >5xULN not recommended.	**Bilirubin /µmol/L** / **Dose /mg/m^2** < 26 / 135 27-51 / 75 >51 / 50 If bilirubin < 1.25 x ULN and transaminase < 10 x ULN, dose at 175 mg/m^2
Pentostatin	Only a small amount is metabolised. It is primarily excreted unchanged by the kidneys - 30 – 90% excreted by kidneys within 24 hours.	**SPC (Hospira 2009)** – Because of limited experience treating patients with abnormal liver function, treat with caution.	Consider dose reduction, but no formal recommendations.
Pemetrexed	Not metabolised to an appreciable extent. Mainly excreted (70-90%) unchanged in the urine.	**SPC (lilly 2009)** - No relationships between AST, ALT ,or total bilirubin and pemetrexed pharmacokinetics were identified. However patients with hepatic impairment such as bilirubin >1.5 x ULN and/or transaminase > 3.0 x ULN (hepatic metastases absent) or > 5.0 x ULN (hepatic metastases present) have not been specifically studied.	Clinical decision

Drug	Pharmacokinetics	Available Information	Recommendation
Procarbazine	After oral absorption, the drug appears to be rapidly and completely absorbed. Procarbazine is metabolised by microsomal enzymes in the liver to an active alkylating agent. After 24hrs up to 70% of a dose is recovered in the urine.	**SPC (Cambridge Labs 2006)** – Caution advisable in patients with hepatic dysfunction. **BC Cancer Agency** – if bilirubin is > 50 µmol/L, dose reduce. **Koren et al**[4] suggest if bilirubin >85µmol/L or AST >180 units, then omit dose.	If bilirubin >50µmol/L, consider a dose reduction. If bilirubin >85µmol/L or AST >180 units, then CI.
Raltitrexed	Not metabolised. 40-50% is excreted unchanged in the urine. 15% of dose is excreted in the faeces over a 10-day period. Active tubular secretion may contribute to the renal excretion.	**SPC (Astra Zeneca 2002**) – No dose adjustment with mild to moderate impairment. Due to some excretion via the faecal route, treatment is not recommended in patients with severe hepatic impairment. **AstraZeneca** – Studies included patients with mild to moderate impairment. Patients with severe impairment were excluded and therefore no information. Liver metastases do not necessarily indicate impairment as 80% of all trial patients had liver metastases and responded well to treatment. No need to dose reduce in this group of patients unless AST/ALT >5xULN. In patients without liver metastases, treat if bilirubin <1.5xULN or AST/ALT <2.5xULN. (Patients were ineligible for trials outside of these ranges). **BC Cancer Agency** – if pre-existing bilirubin is < 10 x ULN, give 100% dose. If drug induced then delay dose. Use not recommended if bilirubin>10XUNL.	If AST/ALT < 5xULN or bilirubin < 10 xULN, treat at 100% dose.
Rituximab	Mean serum $t^1/_2$ increases with dose and repeat dosing: 76.3 hours after 1st infusion and 205.8 hours after 4th infusion. Detectable in body for 3-6 months.	**SPC (Roche 2008) –** No dose reductions are recommended when given in combination with CHOP or CVP chemotherapy, standard dose reductions for chemotherapeutic medicinal products should be applied. **BC Cancer Agency** – no dose adjustment required.	Probably no dose reduction necessary.
Temozolomide	Temozolomide is rapidly and completely absorbed with 100% bioavailability. Tissue distribution is extensive. t½ is ~1.8hrs. The major route of elimination is renal. ~5-10% is excreted unchanged and the remainder as metabolites.	**SPC (Schering Plough 2009)** – the pharmacokinetics of temozolomide were comparable in patients with normal hepatic function and in those with mild or moderate hepatic function. No data is available for severe hepatic impairment. Based on pharmacokinetic properties of temozolamide, it is unlikely that dose reductions are required in patients with severe hepatic dysfunction. **Schering-Plough** – 38% of patients in clinical trials had grade I-IV raised LFTs, in particular ALP. A reduction in dose or discontinuation of drug allowed LFTs to return to normal. **BC Cancer Agency** – No adjustment required	Probably no dose reduction necessary.
Thalidomide	Exact metabolism is unknown. Possible spontaneous hydrolysis in the plasma. 0.7% excreted unchanged in the urine. There is minimal hepatic metabolism and urinary excretion of thalidomide.	**Pharmion** – Doses in patients with hepatic impairment should be titrated with observed tolerance and toxicity and the highest tolerated dose should be selected. **BC cancer agency –** No adjustment required.	No adjustment required.

Drug	Pharmacokinetics	Available Information	Recommendation
Thioguanine	Variable and incomplete oral absorption with 14-46% bioavailability. Extensive metabolism in the liver and other tissues to several active and inactive metabolites. 24-46% of the dose is excreted in the urine within 24 hours.	**SPC (GSK 2008)** – Consideration should be given to reducing the dosage in patients with impaired hepatic function. **BC Cancer Agency** – Dose reduction required but no information.	Consider dose reduction, but no formal recommendations.
Thiotepa	Metabolised in liver to triethylene phosphoramide (TEPA). Only traces of unchanged thiotepa and (TEPA) are excreted in the urine, together with a large proportion of metabolites. (60% within 72 hours).	**SPC (Cyanamid 2004)** – Use lowest possible dose when there is existing hepatic damage and only use if benefit outweighs risk. **Goldshield** – Use with extreme caution in hepatic failure and only in cases where benefit outweighs risk. Start at lowest possible effective dose and use careful monitoring. **BC Cancer Agency**- Dose reduction required but no information.	Lack of information available. Consider dose reduction, but no formal recommendations
Tipifarnib	Currently unknown.	**Ortho Biotech –** No clinical studies have been conducted in subjects with hepatic impairment. Population pharmacokinetic studies show no relationship between the oral clearance and liver enzyme elevation. Total bilirubin concentrations exhibit a weak but statistically significant relationship with tipifarnib clearance.	Clinical decision
Topotecan	Undergoes reversible, pH-dependent hydrolysis of the active lactone moiety to the inactive hydroxyacid (carboxylate) form. A relatively small amount of topotecan is metabolised by hepatic microsomal enzymes to an active metabolite, *N*-demethyltopotecan. The clinical significance of this metabolite is not known. Excretion via biliary and renal route. 20-60% is excreted in the urine as topotecan or the open ring form.	**SPC (GSK 2009)** – There is no experience of topotecan in patients with severely impaired hepatic function (bilirubin >170µmol/L). Plasma clearance in patients with bilirubin 34-170µmol/L decreased by ~10%. t½ was increased by ~30%. **O'Reilly et al[10] -** 21 patients with hepatic dysfunction were studied. Toxicity and pharmacokinetic profiles were similar to those seen in patients without impairment. The clearance was also unaffected. **BC Cancer Agency**- No adjustments required if bilirubin <170 µmol/L, above this no information found.	Lack of information available. Bilirubin <170µmol/L – 100% dose. Bilirubin >170µmol/L – clinical decision.
Trastuzumab	Distributes to normal cells, tumour cells and serum where HER2 antigens are found. $t^1/_2$ = 28.5 days. Remains in body for 24 weeks. Doesn't require hepatic or renal metabolism for elimination.	**SPC (Roche 2008) –** Dedicated studies in patients with renal or hepatic impairment have not been carried out. However, in a population pharmacokinetic analysis, renal impairment was not shown to affect trastuzumab disposition. **BC Cancer Agency** – No dose reduction required.	Probably no dose reduction necessary.

Drug	Pharmacokinetics	Available Information	Recommendation
Treosulphan	Treosulfan is a pro-drug of a bifunctional alkylating agent. High and relatively constant bioavailability. The mean urinary excretion of the parent compound is ~15% over 24hrs.	**SPC (medac GmbH 2008)** – No information. **Medac** – No information.	Lack of information available. Clinical decision
UFT (Tegafur-uracil)	Maximum absorption levels reached within 1-2hrs. Conversion of tegafur to 5-FU occurs via microsomal (CYP2A6) and cytosolic enzymes. The metabolism of 5-FU follows the natural pathways for uracil. Less than 20% of tegafur is excreted intact into the urine. The 3 hydroxy-metabolites are excreted in the urine.	**SPC (Merck sorono 2008)** – Use with caution in patients with renal or hepatic impairment. Since hepatic disorders have been reported, liver function should be monitored during treatment in patients with mild to moderate hepatic dysfunction. Contraindicated in patients that have a known deficiency of hepatic CYP2A6 or severe hepatic impairment. **BMS** – UFT is contra-indicated in patients who have severe hepatic impairment. Since hepatic disorders, including fulminant hepatitis, have been reported in patients receiving single agent UFT, appropriate testing should be performed on any patient receiving the UFT / folinate combination who presents signs and symptoms of hepatic impairment.	Clinical decision
Vinblastine	Vinblastine is extensively metabolised, primarily in the liver to desacetylvinblastine, which is more active than the parent compound. 33% of the drug is slowly excreted in the urine and 21% in the faeces within 72 hours.	**SPC (Hospira 2004)** - Liver disease may alter the elimination of vinblastine in the bile, markedly increasing toxicity to peripheral nerves and necessitating a dosage modification in affected patients. **SPC (Lilly)** – As vinblastine is excreted principally by the liver, it may be necessary to reduce initial doses in the presence of significantly impaired hepatic or biliary function. If bilirubin >51µmol/L, 50% dose is recommended. ● It has been suggested that if bilirubin 26-51µmol/L or AST / ALT 60-180 units give 50% dose. If the bilirubin >51µmol/L or AST /ALT >180 units, the drug is not given[11]. **BC Cancer Agency**: Bilirubin 25-50 µmol/L – give 50% of dose, grater than 50 µmol/L give 25% of dose	**Bilirubin /µmol/L** / **AST/ALT /units** / **Dose** 26-51 or 60-180 50% >51 & N 50% >51 & >180 omit
Vincristine	Metabolised by cytochrome P450 (in the CYP 3A subfamily). Elimination is primarily biliary - excreted into bile and faeces (67% within 72 hours, 40-50% as metabolites). 10% excreted in urine in 24hrs.	**SPC (Hospira 2004)** – Patients with liver disease sufficient to decrease biliary excretion may experience an increase in the severity of side-effects. A 50% reduction is recommended for patients with a bilirubin >51µmol/L. **Lilly** – as SPC ● It has been suggested that if bilirubin 26-51µmol/L or AST / ALT 60-180 units, give 50% dose. If the bilirubin >51µmol/L or AST /ALT >180 units, the drug is not given[11]. **UKALL 2003 guidelines** state that LFTs should only be checked if the patient is jaundiced. Withhold if total bilirubin >50µmol/L. Administer 50% of dose if total bilirubin is 25-50 µmol/L. Do not alter dose for abnormal transaminases. **BC Cancer Agency** – Bilirubin 26-50µmol/L-50% of dose, >50µmol/L then 25% of dose.	**Bilirubin /µmol/L** / **AST/ALT /units** / **Dose** 26-51 or 60-180 50% >51 & N 50% >51 & >180 omit

Drug	Pharmacokinetics	Available Information	Recommendation
Vindesine	Metabolised by cytochrome P450 (in the CYP 3A subfamily). Elimination is primarily biliary. (13% excreted in urine in 24hrs).	**SPC** (Genus 2004) – Excreted principally by the liver, therefore may be necessary to reduce initial doses in the presence of significantly impaired hepatic or biliary function.	Consider dose reduction in severe hepatobiliary impairment.
Vinorelbine	Metabolism appears to be hepatic. t½ is greater than 40hrs. Excretion is mainly by the biliary route (18.5% appears in the urine).	**SPC (Medac GmbH 2007)** – Vinorelbine metabolism and clearance are mostly hepatic. In breast cancer patients, clearance is not altered in presence of moderate liver metastases (i.e. <75% of liver volume replaced by the tumour). In these patients there is no pharmacokinetic rationale for reducing doses. In patients with massive liver metastases (i.e. >75% of liver volume replaced by the tumour), it is suggested that the dose is reduced by 1/3 and the haematological toxicity closely followed. **Pierre Fabre** – For patients presenting with severe liver impairment (bilirubin> 2xUNL and/or transaminases > 5xUNL), it is suggested that the dose be reduced by 33% and the haematological parameters be closely monitored since the maximum dose which was evaluated in this subset of patients was 20mg/m^2. **BC Cancer Agency** – Bilirubin 36-50 µmol/L – 50% of dose, >50µmol/L then 25% of dose.	**AST/ALT** >5 x UNL **Bili** >2 x UNL **Dose** Reduce by 1/3

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