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Dosage Adjustment for Cytotoxics in Renal 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. As limited data is available, the scope of the document applies to adult data. If paediatric data is obtainable, this has been included. If a patient is following a specific clinical trial or protocol, it is advisable to follow the associated dose modifications.

The BNF (Edition 59) states (from Chronic kidney disease in adults: UK guidelines for identification, management and referral (March 2006):

Degree of Impairment	**eGFR mL/min/1.73m^2 (GFR = eGFR x BSA/1.73)**
Normal	More than 90 (with other evidence of kidney damage)
Mild	60 – 89 (with other evidence of kidney damage)
Moderate	30 – 59
Severe	15 – 29
Established renal failure	Less than 15

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 renal impairment. **Schering** – Unlikely to require a reduction. Cleared intracellularly. Treatment is not recommended. **BC Cancer Agency –** No information found.	Clinical Decision
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 2007)** – for patients with impaired renal function, reduce dose by 20-30% (to 60-75mg/m^2 per day). **BC Cancer Agency –** Reduce dose by 25% if serum creatinine is >140µmol/L **AML 17** - If renal function is reduced (Cr Cl < 60ml/min) the dose should be reduced by 25%. **Dialysis** **Renal Drug Handbook** - CAPD, HD, HDF/High flux, CAV/VVHD - Dose as in renal impairment – 60-75mg/m^2 daily.	If CrCl < 60ml/min, reduce dose by 25%

Drug	Pharmacokinetics	Available Information	Recommendation
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 urine.	**SPC (Cephalon 2008) –** Safety and effectiveness of arsenic trioxide in patients with renal impairment have not been studied. Caution is needed in patients with renal impairment as this is the main route of elimination. **Cephalon –** A phase I, multicentre, open label, non-randomised study of arsenic trioxide injection was performed to establish the safety of the drug in patients with renal impairment. Twenty patients with varying renal function were included. Patients that had severe renal dysfunction (GFR<30mls/min) had a mean AUC value 48% greater than patients with normal renal function. Systemic exposure to metabolites of arsenic trioxide was also greater in the renally impaired groups of patients. No increased toxicity was noted but the clinical consequences were unknown. Toxicity profile across all groups of renal impairment was similar.	Clinical decision – consider dose reduction in GFR<30mls/min.
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 on patients with renal insufficiency, reduce dose to 25mg/m2 as a precautionary measure. **BC cancer agency** – as above.	Reduce dose to 25mg/m2 in renal impairment.
Azacitadine	Azacitadine undergoes rapid elimination. The route of elimination requires further study. The drug appears to undergo metabolism. Excretion of unchanged drug and metabolites is via the kidneys. The activity of metabolites is unknown.	**Pharmion –** Recommended starting dose is 75mg/m2 SC daily for 7 days. No dose adjustment of initial dose based on renal function is recommended. If unexplained reductions in serum bicarbonate or elevations in serum creatinine, or BUN occur, the dosage should be reduced by 50% on the next course. The start of the next cycle should be delayed until values return to normal.	No dose reductions necessary for 1st cycle.
Bevacizumab	Terminal half-life 19-20 days	**SPC (Roche 2008) –** Safety and efficacy has not been studied in this group of patients **Roche –** preclinical studies in animal models indicated no adverse effects in renal dysfunction. **Dialysis** **Inauen et al** reported a case where bevacizumab was well tolerated with haemodialysis without a dose reduction[1]. **Renal Drug Handbook** – bevacizumab has been used in a haemodialysis patient at a dose of 5mg/kg every 14 days.	Clinical decision
Bexarotene	Metabolised by oxidation via CYP450 3A4 and glucuronidation. Less than 1% excreted in the urine.	**SPC (Cephalon 2007) –** No formal studies have been performed in this group of patients. Renal excretion is not a significant elimination pathway.	Clinical decision – unlikely to require reduction unless severe renal impairment.

Drug	Pharmacokinetics	Available Information	Recommendation
Bleomycin	t½ 2-4 hours. Rapid distribution to body tissues (highest conc^{n} in skin, lungs, peritoneum & lymph). Inactivation takes place primarily in the liver. ~ 2/3 of drug is excreted unchanged in the urine, probably by glomerular filtration.	**SPC (Mayne pharma)** – If creatinine 177-354µmol/L, give 50% dose. If creatinine >354µmol/L, further reduction is necessary. The rate of excretion is highly influenced by renal function; concentrations in plasma are greatly elevated if usual doses are given to patients with renal impairment with only up to 20% excreted in 24 hours. Observations indicate that it is difficult to eliminate bleomycin by dialysis. **Kyowa Hakko** – As above and bleomycin should be used with caution in patients with significant renal impairment as clearance may be reduced and toxicity increased. NB when GFR ~<30ml/min patient may be at increased risk of developing lung dysfunction. **Faulding** – suggested dose modification schedule: CrCl 10-50ml/min – 75% dose. CrCl < 10ml/min, give 50% dose. **Renal Drug Handbook** – GFR 20-50mls/min - dose as in normal renal function, 10-20mls/min give 75% of dose, <10mls/min – 50% of normal dose. **Dialysis** **Renal Drug Handbook** – CAPD, HD, HDF/High Flux – 50% dose. CAV/VVHD – 75% dose.	**CrCl (ml/min)** **Dose** >50 100% 10-50 75% <10 50%
Bortezomib	Metabolised by oxidative debronation via CYP450 3A4, 2C19 and 1A2. Small amount excreted in the urine. Terminal t½ is 9-15 hours.	**SPC (Janssen Cilag 2008) –** The pharmacokinetics of bortezomib are not influenced in patients with renal impairment (CrCl> 20 ml/min/1.73 m^2); therefore, dosing adjustments are not necessary for these patients. It is unknown if the pharmacokinetics are influenced in patients with severe renal impairment **(**CrCl < 20 ml/min/1.73m^2 not undergoing dialysis). Since dialysis may reduce bortezomib concentrations, the drug should be administered after the dialysis procedure. **BC Cancer Agency –** Use with caution in renal impairment. **Renal Drug Handbook** – GFR 30-50ml/min dose as in normal renal function, GFR 10-30ml/min dose as in normal renal function. Monitor carefully. GFR<10 a reduced dose may be required. Normal doses have been used in GFR 10-30ml/min with increased risk of adverse effects. Some trials have used doses of 1mg/m2 in patients with GFR 10-30ml/min with similar efficacy and incidence of side effects. **Dialysis** **Renal Drug Handbook –** CAPD, HD, HDF/High flux –Consider dose reduction. CAV/VVHD – Dose as in normal renal function.	Clinical decision – consider reduction if GFR<20mls/min

Drug	Pharmacokinetics	Available Information	Recommendation
Busulfan	The mean elimination t½ is 2.57hrs. Extensive hepatic metabolism to at least 12 methanesulfonic acid, and 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 inactive metabolite.	**SPC (Pierre Fabre 2008)** – Studies have not been conducted in renally impaired patients. Caution is recommended in this group. **Glaxo Wellcome** – although very little unmetabolised drug is excreted in the urine, a complex range of metabolites are excreted by this route. The administration of high-dose busulphan has been evaluated in 15 patients with multiple myeloma (4 had CrCl < 30ml/min) with no problems[2]. **BC Cancer Agency** – no information found **Dialysis** **Ullery et al, 2000**- A published case report demonstrated that haemodialysis effectively cleared busulfan. Exposure to busulfan was not significantly altered[3]. **Renal Drug Handbook** – CAPD, HD, HDF/High flux. CAV/VVHD – Dose as in normal renal function.	No dose reduction necessary.
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)** – capecitabine is contra-indicated in patients with severe renal impairment (CrCl <30 ml/min) The incidence of grade 3-4 toxicities in patients with moderate renal impairment (CrCl 30-50 ml/min) is increased. An initial dose of 75% of the 1250mg/m^2 starting dose is recommended. In patients with mild renal impairment (CrCl 51-80ml/min), no adjustment of the starting dose is recommended. Careful monitoring and prompt treatment interruption is recommended if the patient develops a grade 2, 3, or 4 adverse event, followed by the appropriate dose adjustment. **Dialysis** **Renal Drug Handbook -** CAPD, HD, HDF/High flux. CAV/VVHD – Avoid	**CrCl (ml/min)** **Dose** 51-80 100% 30-50 75% <30 CI
Carboplatin	There is little, if any, true metabolism of 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)** – Dose reduce with renal impairment and monitor haematological nadirs and renal function. Myelosuppression is closely related to renal clearance. Carboplatin is contra-indicated with CrCl <20ml/min. **Faulding** – CrCl >40ml/min, max dose = 400mg/m^2 CrCl 20-39ml/min, max dose = 250mg/m^2 **Dialysis** **BC Cancer Agency –** In dialysis dependant chronic renal failure give a fixed dose of 100mg, if the patient has had previous platinum treatment, or 150mg if not. Dialysis should be performed 24 hours after the dose. **Renal Drug Handbook** – CAPD, HD, HDF/High flux. CAV/VVHD - Dose as in normal renal function.	Dose using Calvert equation: Dose = AUC(25 + GFR) CI if CrCl <20ml/min

Drug	Pharmacokinetics	Available Information	Recommendation
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 2007)** – no information. **BMS** – very little information. Clinical decision based on the haematological response to previous doses and monitoring blood counts. **Kintzel et al**[4] suggest for CrCl of 60ml/min; use 0.8 fraction of dose, for CrCl of 45ml/min, use 0.75 fraction of dose, for CrCl of 30ml/min, carmustine is not recommended **BC Cancer Agency** - GFR <10ml/min discontinue **The Renal Handbook** – dose as in normal function. **Dialysis** **BMS –** Carmustine is not dialysed. Dose adjustment is not required in patients undergoing renal replacement therapy. Includes CAPD, HD, and continuous arterio-venous/veno-venous haemodiafiltration[5]. **Boesler et al, 2005-** documented cases where carmustine was used with a dose reduction in patients having haemodialysis. Doses escalated and reduced depending on white cell count[6]. **Renal Drug Handbook** – CAPD, HD, HDF/High flux. CAV/VVHD - Dose as in normal renal function.	**CrCl (ml/min)** **Dose** 60 80% 45 75% <30 Clinical decision **Dialysis** – reference source suggests that no dose reduction required. This is confirmed by various renal handbooks, however, dose reductions are recommended for patients with renal impairment in these handbooks. Therefore, clinical decision.
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 renal function have been investigated. **Merck** – No recommended dose adjustment, not studied in this group of patients, not contraindicated. **Dialysis** **Inauen et al** reported a case where cetuximab was well tolerated with haemodialysis without a dose reduction [1]. **Renal Drug Handbook** – CAPD, HD, HDF/High flux. CAV/VVHD - Not dialysed, dose as in normal renal function.	Clinical decision – unlikely to require a reduction.
Chlorambucil	Good oral absorption - absorption slowed and decreased by 10-20% if ingested with food. Metabolism predominantly in liver via hepatic microsomal enzyme oxidation system. <1% excreted unchanged in the urine. t½ = 2 hours.	**SPC (GSK 2007)** – monitor patients with evidence of impaired renal function as prone to additional myelosuppression associated with azotaemia. **Glaxo Wellcome** – very little information. Renal function does not appear to affect the elimination rate. Chlorambucil is unlikely to be dialysed. **Renal Drug Handbook** – no dose reduction necessary. **BC Cancer Agency** – increased risk of myelosuppression **Dialysis** **Renal Drug Handbook** – CAPD, HD, HDF/High flux. CAV/VVHD - Dose as in normal renal function.	No dose reductions necessary, however, monitor patients carefully, as they are more prone to myelosuppression. **Dialysis** – not dialysed, dose as in normal renal function.

Drug	Pharmacokinetics	Available Information	Recommendation
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 drug is excreted unchanged in the urine. 50% 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)** – Cisplatin induces nephrotoxicity, which is cumulative. It is therefore contra-indicated in patients with renal impairment. **Kintzel et al**[4] suggest for CrCl of 60ml/min; use 0.75 fraction of dose, for CrCl of 45ml/min, use 0.5 fraction of dose, for CrCl of 30ml/min cisplatin is contra-indicated. **BC Cancer Agency –**GFR>60mls/min ; 100%, GFR 45-59mls/min; 75% dose, <45mls/min ; hold cisplatin- delay with hydration/switch to carboplatin. **Bennett et al**[7] – GFR >50mls/min 100% dose; GFR 10-50mls/min 75% dose GFR <10mls/min 50% dose **Dialysis** **Haemodialysis** – Dialysed. Give 50% dose[7] NB. There is experience of using the same dose as the GFR. It should be noted, however, that there is no evidence for this practice. **BC Cancer Agency** -Advises dialysis within 3 hours of giving dose.	**GFR (ml/min)** **Dose** >60 100% 45-59 75% <45 consider carboplatin Consider carboplatin if GFR <45ml/min Conflicting information. Where GFR is less than 45mls/min - clinical decision. **Dialysis** – give 50% dose. Dialysis should be performed within 3 hours after giving dose.
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 (Janssen Cilag 2008)** – Acute renal insufficiency has developed in some patients receiving high doses of cladribine. There is inadequate data on dosing of patients with renal insufficiency. **SPC (Lipomed GmbH 2008)** - Contraindicated in moderate to severe renal impairment (CrCl</=50ml/min) **Janssen-Cilag** – very limited information available. In a small study (n=9), it was found that less than 30% of cladribine was excreted in the urine and less than 10% was excreted as metabolite.	Lack of information available. Clinical decision
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 this group of patients (serum creatinine >2xUNL). Due to mechanism of excretion use with caution in mild to moderate renal impairment and the drug is contraindicated in severe renal impairment**.** **Bioenvision –** as above	Clinical decision likely to require dose reduction. Contraindicated in severe renal impairment.

Drug	Pharmacokinetics	Available Information	Recommendation
Crisantaspase	Plasma t½ is 7-13 hours.	**SPC (Opi 2005) –** no contraindications in renal impairment **UKALL2003** – no dose modifications listed for renal impairment	Clinical decision – unlikely to require modification.
Cyclophosphamide	Pro-drug – converted by hepatic microsomal enzymes to alkylating metabolites (great inter-patient 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 creatinine >120μmol/L. **Astra Medical** - Patients with impaired renal function have been reported to show an increase in metabolite concentration. Cyclophosphamide and its metabolites can be eliminated by haemodialysis. Availability of mesna in the urinary tract depends on renal function. **Lam et al** [8]– If CrCl > 10 ml/min, give 100% dose. **Renal Drug Handbook** – 20-50 mls/min dose as in normal renal function, 10-20mls/min 75-100% of normal dose,<10 50-100% of normal dose. **BC Cancer Agency** –<10mls/min 75% dose otherwise 100%. **Dialysis** **Baxter (Prev Asta Medical) –** it is known that cyclophosphamide and its alkylating metabolites can be eliminated by dialysis.[9,10,11,12,13] In case of complete anuria, neither cyclophosphamide, nor its metabolites should appear in the urinary tract. The use of mesna concomitantly may therefore be unnecessary in anuric patients. If there is *any* risk of cyclophosphamide or its metabolites entering the urinary tract, mesna should probably be given to prevent urothelial toxicity. It should be noted that *complete* anuria is extremely rare.	**GFR (ml/min)** **Dose** >20 100% 10-20 75% <10 50% Clinical decision – consider whether patient is being treated with high dose treatment. **Dialysis** **Renal Drug Handbook** -dose at 50-100% dose (CAPD, HD and HDF/High flux) Do not perform dialysis for 12 hours. Dose at 75-100% dose (CAV/VVHD). If anuric, mesna may not be required.
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 the urine, but some in the bile.	**SPC (Hospira 2007)** – Dose reduction does not appear to be necessary in patients with impaired renal function. The human liver apparently detoxifies a substantial fraction of the administered dose. **Faulding** – When using high dose cytarabine (1-3g/m^2) reduced doses should be considered in patients with renal impairment[7]. **Pfizer** – Dose reductions are not necessary when standard doses are used (100-200mg/m2/24hrs). Reduced doses should be considered when using high dose cytarabine in these patients. **BC Cancer Agency** – for high dose therapy the following reductions should be followed to reduce the risk of neurotoxi95city as this is directly associated with renal function. See recommendations. **Dialysis** **Renal Drug Handbook** – CAPD, HD, HDF/High flux, CAV/VVHD – full dose for low dose regimes. Avoid in high dose regimes.	No dose reduction necessary **High Dose 1- 3g/m^2:** **GFR (ml/min)** **Dose** >60 100% 46-60 60% 31-45 50% <30 CI

Drug	Pharmacokinetics	Available Information	Recommendation
Dacarbazine	Dacarbazine (DTIC) is assumed to be inactive. Microsomal metabolism in the liver produces 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 there is mild to moderate renal or hepatic insufficiency alone, a dose reduction is not usually required. In patients with combined renal and hepatic impairment elimination of dacarbazine is prolonged. However, no validated recommendations on dose reductions can be given currently. **Faulding** – As the drug is excreted 50% unchanged in the urine by tubular secretion, impairment of renal function is likely to necessitate a change in dosage. **Kintzel et al**[4] suggest for CrCl of 60ml/min; use 0.8 fraction of dose, for CrCl of 45ml/min, use 0.75 fraction of dose, for CrCl of 30ml/min, use 0.7 fraction of dose. **Medac UK** – Recommend dose adjustments as described by Kintzel et al. **Renal Drug Handbook** – See recommendations. **Dialysis** **Renal Drug Handbook** - CAPD, HD, HDF/High flux. CAV/VVHD – 70% dose	**CrCl (ml/min)** **Dose** 45-60 80% 30-45 75% <30 70%
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 information. **BC Cancer Agency** – No adjustment required. **Renal Drug Handbook –** Dose as in normal renal function, use with caution. **Dialysis** **Renal Drug Handbook –** CAPD, HD, HDF/High flux. CAV/VVHD - Dose as in normal renal function.	Clinical decision – unlikely to require a reduction.
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 2009) –** Not studied in this group of patients but Since the renal clearance of dasatinib and its metabolites is < 4%, a decrease in total body clearance is not expected in patients with renal insufficiency. **Renal Drug Handbook –** Dose as in normal renal function, use with caution. **Dialysis** **Renal Drug Handbook –** CAPD, HD, HDF/High flux. CAV/VVHD - Dose as in normal renal function.	Unlikely to require reduction
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 2008**) – A dose reduction is recommended in patients with impaired renal function. See recommendations **Aventis** – as SPC **BC Cancer Agency** – Reduce dose by 50% if creatinine is greater than 265 µmol/L **Dialysis** **The Renal Handbook** – CAPD, HD, CAV/VVHD - unlikely to be dialysed	**Creatinine /µmol/L** **Dose** <105 100% 105-265 75% >265 50%

Drug	Pharmacokinetics	Available Information	Recommendation
Docetaxel	Cytochrome P-450 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)** – No information **Aventis** – No dose adjustment necessary. 1 major and 3 minor metabolites have been identified and these are excreted in the faeces. **Dialysis** **Mencoboni et al, 2006** reported a case where the pharmacokinetics of docetaxel, pre and post-dialysis administration in a haemodialised patient were investigated. The results showed no apparent differences in the plasma concentration-time curves of docetaxel administered before or after dialysis. The authors concluded that docetaxel can be used in dialysis patients, with no dosage reduction needed, with docetaxel not being removed from the blood during dialysis[14]. **Renal Drug Handbook**- CAPD, HD, HDF/High flux. CAV/VVHD - unlikely dialysability – dose as in normal renal function.	No dose reduction necessary. **Dialysis** Dose as in normal renal function.
Doxorubicin	Mainly metabolised in the liver. 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 (Hameln 2008)** – Since doxorubicin and metabolites are excreted in the urine only to a minor degree, there are no clear indications that the pharmacokinetics or toxicity of doxorubicin are altered in patients with impaired renal function. **Pharmacia** – Yoshida et al[15] have shown that the AUC of doxorubicin and doxorubicinol (active metabolite) is significantly higher in patients with renal failure. This study also suggests special attention should be paid to haemodialysis patients receiving digoxin **BC Cancer agency** – No adjustment required. **Renal Drug Handbook** – No adjustment necessary **Dialysis** **Renal Drug Handbook** - CAPD, HD, HDF/High flux. CAV/VVHD – dose as in normal renal function.	No dose reduction required. Clinical decision in severe impairment.
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 (Hameln 2008)** – Moderate renal impairment does not appear to require a dose reduction in view of the limited amount excreted by this route. Lower starting doses should be considered in patients with severe renal impairment (serum creatinine > 450 µmol/l). **BC Cancer Agency –** lower starting doses recommended if serum creatinine >442µmol/L **Renal Drug Handbook –** Dose as in normal renal function unless GFR<10ml/min –then consider a dose reduction**.** **Dialysis** **Renal Drug Handbook** – CAPD, HD, HDF/High flux. CAV/VVHD – dose as in normal renal function.	Dose reduce in severe impairment only. Clinical decision.

Drug	Pharmacokinetics	Available Information	Recommendation
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 renal impairment. **BC Cancer Agency** – No adjustment required. **Dialysis** **Renal Drug Handbook** – CAPD, HD, HDF/High flux. CAV/VVHD – dose as in normal renal function. Use with caution.	Probably no adjustment needed – 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. Up to 16% recovered in the faeces.	**SPC (medac GmbH 2007)** – If GFR - >50ml/min ; 100% dose, 15-50mls/min; 75% dose, no specific information for GFR< 15ml/min however further dose reduction should be considered. Subsequent etoposide dosing should be based on patient tolerance and clinical effect. **BMS** – Creatinine clearance is the strongest predictor of etoposide clearance. US prescribing information suggest a 25% dose reduction for GFR between 15–50 ml/min[16]. Subsequent dosing should be based on patient tolerance and clinical effect. A further dose reduction should be considered with GFR<15ml/min. **Kintzel et al**[4] suggest for CrCl of 60ml/min; use 0.85 fraction of dose, for CrCl of 45ml/min, use 0.8 fraction of dose, for CrCl of 30ml/min, use 0.75 fraction of dose. **Textbook of drug prescribing in renal failure and BC Cancer Agency** – GFR 10-50ml/min; 75% dose. Below 10 = 50% of dose. **Dialysis** **Holthius et al**[17] reported comparable pharmacokinetics in patients receiving haemodialysis for doses of etoposide up to 127mg/m^2 in relation to patients with normal renal function. **Sauer et al**[9] and **Brindley et al**[18] found that etoposide is not removed by dialysis. **Renal Drug Handbook** – CAPD, HD, HDF/High flux. CAV/VVHD – 50% dose then base on clinical response.	**CrCl (ml/min)** **Dose** >50 100% 15-50 75% <15 50% Subsequent doses should be based on clinical response. **Dialysis** Start at reduced dose and increase according to clinical response.
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 May 2008)** – If CrCl 30-70ml/min, then dose should be reduced by up to 50% and close haematological monitoring should be used to monitor toxicity. If CrCl <30 ml/min, fludarabine is contra-indicated. **Schering** – as SPC **BC Cancer Agency –** as SPC **Renal Drug Handbook** – GFR 30-70mls/min use 50-75% of dose, 10-30mls/min use 50-75% of dose but use with care. GFR<10mls/min use 50% of dose and use with care. **Dialysis** **Renal Drug Handbook** – CAPD, HD, HDF/High flux. – 50% dose, use with care. CAV/VVHD – 50-75% dose, use with care.	**CrCl (ml/min)** **Dose** >70 100% 30-70 50% <30 CI

Drug	Pharmacokinetics	Available Information	Recommendation
Fluorouracil	Fluorouracil is distributed through the body water. Activated in target cells, catabolized in 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.	**SPC (Medac GmbH 2007)** – Fluorouracil should be used with caution in patients with reduced renal function. **Faulding** –Bennett et al[7] suggested that no dose adjustment is needed in renal impairment. **BC Cancer Agency –** No adjustments required **Dialysis** **Renal Drug Handbook** – CAPD, HD, HDF/High flux. CAV/VVHD – dose as in normal renal function..	Consider dose reduction in severe renal impairment only.
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 (Eli Lilly 2007**) – Use with caution in patients with impaired renal function. **Lilly** – Since gemcitabine is extensively metabolised by various tissues, mild to moderate renal insufficiency would not be expected to significantly affect its clearance, although there is a possibility of accumulation of the inactive metabolite, dFdU. Lilly investigated the Pharmacokinetics in 18 patients with renal insufficiency and found that there was no significant difference between patients on the basis of their GFR (GFR ranged from 30ml/min upwards). **Dialysis** Conventional intermittent haemodialysis should be performed before a weekly dose and again some 48 hours later. Provided this is carried out the patient should not face excess toxicity. **Renal Drug Handbook** – Likely to be dialysed by CAPD, HD, CAV/VVHD, HDF/High Flux.	CrCl>30ml/min – standard dosing CrCl<30ml/min – consider dose reduction – clinical decision. **Dialysis** Likely to be dialysed but no information on dosing.
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.	**No UK licence** **Wyeth pharmaceuticals-** The efficacy and safety profile of gemtuzumab ozogamicin in patients with renal function impairment is relatively unknown. One case report has shown success without excessive toxicity in a patient receiving haemodialysis thrice weekly; however, more evidence is needed to support its use in this patient population. There are no specific recommendations for monitoring patients with renal impairment receiving gemtuzumab ozogamicin therapy.	Clinical decision

Drug	Pharmacokinetics	Available Information	Recommendation
Hydroxycarbamide (Hydroxyurea)	After oral administration, hydroxyurea is readily absorbed from the GI tract. 50% hepatically metabolised. Peak plasma conc^{n} are reached by 2hrs. 50% of a 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 (E.R Squibb 2006) -** Use with caution in patients with marked renal dysfunction. **BMS** – Kintzel et al[4] suggest for CrCl of 60ml/min; use 0.85 fraction of dose, for CrCl of 45ml/min, use 0.8 fraction of dose, for CrCl of 30ml/min, use 0.75 fraction of dose. Bennett et al[19] suggest reducing the dose by half in patients with GFR <10ml/min. **Renal Drug Handbook** – GFR >60mls/min – give 85% of dose, 45-60mls/min, 80%dose, 30-45mls/min, 75% dose, 10-30ml/min, 50% dose, <10ml/min 20% dose. Titrate according to response. **BC Cancer Agency-** GFR >50ml/min- 100%; 10-50- 50% ;<10 - 20% **Dialysis** **Renal Drug Handbook** - CAPD, HD, HDF/High flux - 20% normal dose and titrate to response. CAV/VVHD - 50% normal dose and titrate to response.	**CrCl (ml/min)** — **Dose** >60 — 85% 45-60 — 80% 30-45 — 75% 10-30 — 50% <10 — 20% .
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 Cr >177µmol/L. For other anthracyclines, 50% dose reduce if Cr in range 106-177 µmol/L. Contra-indicated in severe renal impairment. **Pharmacia** – some studies have suggested that patients with Cr levels up to 350µmol/L can be treated with oral idarubicin without dose modification. **BC cancer agency –** Creatinine >200/µmol/L give 50% dose **Dialysis** **Renal Drug Handbook** - CAPD, HD, HDF/High flux – Use 50% of dose with caution. CAV/VVHD - Use 75% of dose with caution..	**Creatinine /µmol/L** — **Dose** <100 — 100% 100-175 — 50% >175 — Clinical decision

Drug	Pharmacokinetics	Available Information	Recommendation
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 2006) – Risk factors to develop an encephalopathy are impaired renal function (creatinine > 132µmol/L). Use is contra-indicated in renal impairment. **Asta Medical** – Dose reduction schedules established for cyclophosphamide (which has similar metabolic pharmacokinetic parameters). Ifosfamide is known to be more nephrotoxic than cyclophosphamide and has a CNS toxicity profile. Availability of mesna in the urinary tract depends on renal function. **Renal Drug Handbook –** GFR 20-50ml/min 75% dose; 10-20ml/min 75% dose; <10ml/min 50% dose. **Euro-EWINGS protocol** – Ifosfamide 9 g/m^2 administered per course. Protocol suggests to treat with 100% dose if GFR ≥ 60 ml/min. If GFR 40-59 ml/min, give 70% dose. If GFR <40 ml/min, use cyclophosphamide instead (1500 mg/m^2). **Dialysis** **Renal Drug Handbook**– CAPD, HD, HDF/High flux use 60% of normal dose. Do not perform dialysis for at least 12 hours. CAV/VVHD use 80% of normal dose. **BC Cancer Agency -** dose as in <10ml/min at least 12 hrs before dialysis.	**GFR (ml/min)** **Dose** >60 100% 40-59 70% <40 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) –** Imatinib and its metabolites are not significantly excreted via the kidney. Since renal clearance of imatinib is negligible, a decrease in total body clearance is not expected in-patients with renal insufficiency, However, in severe renal insufficiency caution is recommended. **BC Cancer Agency** – No adjustment required. **Renal Drug Handbook** – No adjustment to starting dose **Dialysis** **Novartis –** Case reported where imatinib has been used in end stage renal disease while on haemodialysis. The pharmacokinetics of the parent drug and metabolite were not altered. The author concluded the drug is safe to use at full dose [14] for patient on haemodialysis, probably with renal failure **Renal Drug Handbook**– CAPD, HD, HDF/High flux, CAV/VVHD. Dose as in normal renal function.	No adjustment required. **Dialysis** Unlikely to require reduction.
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)** – not recommended in patients with impaired renal function as studies in this population have not been done. **Aventis** – as above **BC Cancer Agency -** No dose adjustment required **Dialysis** **Renal Drug Handbook** – CAPD, HD, HDF/High flux - Reduce dose (50-80 mg/m2) and monitor closely. Increase as tolerated. CAV/VVHD - dose as in normal renal function and monitor closely. **Stemmler et al**[20] - Patient treated with 80mg/m^2 weekly without severe side effects. Haemodialysis with irinotecan seems feasible. May be advisable to start at a low dose e.g. 50mg/m^2 and escalate slowly if tolerated.	No dose reduction needed, however use with caution as no information in this setting.

<table>
<tr><th>Drug</th><th>Pharmacokinetics</th><th>Available Information</th><th>Recommendation</th></tr>
<tr>
<td>Lenalidomide</td>
<td>Substantially excreted via kidneys</td>
<td>Celgene- Dose reductions recommended for multiple myeloma and myelodysplatic syndrome as adverse events have been shown to increase with reduced GFR.
<u>Dialysis</u>
Renal Drug Handbook – CAPD – 15mg 2-3 times a week. HD, HDF/High flux – 15mg 3 times a week post dialysis. CAV/VVHD - dose as in GFR 30-50ml/min.</td>
<td>
<table>
<tr><td>GFR mls/min</td><td>MM</td><td>MDS</td></tr>
<tr><td>>/=50</td><td>25mg od</td><td>10mg od</td></tr>
<tr><td>50<X>/=30</td><td>10mg dose may be increased to 15mg od after 2 cycles if patient not responding</td><td>5mg od</td></tr>
<tr><td><30 without dialysis</td><td>15mg q48hrs</td><td>5mg q48hrs</td></tr>
<tr><td><30 with dialysis</td><td>15mg 3xweek after dialysis</td><td>5mg 3x week after dialysis</td></tr>
</table>
</td>
</tr>
<tr>
<td>Liposomal Daunorubicin</td>
<td>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.</td>
<td>SPC – no information.
Gilead Sciences –From American prescribing information. Where serum Cr >265μmol/L give 50% normal dose. Monitor toxicities in particular cardiotoxicity.</td>
<td>Very little information.
If Cr >265μmol/L, give 50% normal dose.</td>
</tr>
<tr>
<td>Liposomal Doxorubicin</td>
<td>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.</td>
<td>SPC (Schering Plough 2008) – As doxorubicin is metabolised by the liver and excreted in the bile, dose modifications should not be required for liposomal doxorubicin. No information in patients with a GFR<30mls/min</td>
<td>No dose reduction needed.</td>
</tr>
</table>

Drug	Pharmacokinetics	Available Information	Recommendation
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)** – Kidney function should be assessed periodically. Contraindicated in severe renal impairment. **BC Cancer Agency** – if CrCl 10-50 ml/min, give 75% previous dose and if CrCl < 10 ml/min, give 50% previous dose. **Kintzel et al**[4] suggest for CrCl of 60ml/min; use 0.75 fraction of dose, for CrCl of 45ml/min, use 0.7 fraction of dose, for CrCl of 30ml/min, lomustine is not recommended. **Renal Drug Handbook** – GFR 45-60mls/min – 75% of dose, 30-45mls/min give 70% of dose, <30mls/min – not recommended. **Dialysis** **Renal Drug Handbook** – HD, CAPD, HDF/High flux and CAV/VVHD - avoid.	**CrCl (ml/min)** **Dose** >60 100% 45 - 60 75% 30 - 45 50% <30 not recommended
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)** – Clearance, although variable, is decreased in renal impairment. For conventional IV doses (16-40mg/m2) & moderate – severe impairment, reduce initial dose by 50% and subsequent dosage determined by haematological suppression. For high IV doses (100-240mg/m2) and GFR 30-50ml/min, reduce dose by 50% Adequate hydration and forced diuresis are also necessary. High dose melphalan is not recommended in patients with a more severe renal impairment GFR<30mls/min. **GSK** – as above. Some authors have suggested that it is not absolutely necessary to withhold the drug in patients with severe renal impairment. The initial dose should be reduced by 50% and adequate hydration and forced diuresis should be used. Harousseau et al[21] suggest using 60-120mg/m2 (rather than 140mg/m2) if GFR 40-50ml/min **BC cancer agency –** recommended dose adjustments available for non-transplant patients (see recommendations). **Tricot et al**[22] – Addressed safety of autotransplants in patients with a GFR <40ml/min. The dose of 200mg/m^2 was divided into two doses (100mg/m^2/day) and given on two consecutive days. This schedule did not adversely affect the incidence of severe mucositis or overall survival. However, it was associated with longer durations of fever and hospitalisation. **Dialysis** **SPC (GSK 2007)** -High dose melphalan with haematopoietic stem cell rescue has been used successfully even in patients with dialysis dependant end stage renal failure. **Renal Drug Handbook** – CAPD, HD, HDF/High flux – dose as in GFR<10ml/min. CAV/VVHD - dose as in GFR<10-20ml/min. **BC cancer Agency -** Not removed from plasma to any significant degree by hemodialysis, hemoperfusion, or peritoneal dialysis. Continuous arteriovenous hemofiltration (CAVH): administer 75% of usual dose.	GFR 30-50ml/min, give 50% dose. For GFR <30ml/min, clinical decision. Some sources suggest that *not* necessary to withhold high dose therapy – dose may be split on to 2 consecutive days. Suggested Dosing for patients not receiving BMT (IV or oral) GFR >50mls/min, give 100% dose GFR 10-50mls/min, give 75% dose GFR<10mls/min, give 50% dose

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 variations in AUC. It is extensively metabolised (by intracellular activation). At conventional doses clearance is primarily hepatic. Renal clearance may become important at high doses.[11] t½ = 1-3 hrs (PO) and 0.3-1 hr (IV).	**SPC (GSK 2007**) – Monitor renal function in the elderly. Consider reducing dose in impaired renal function **BC Cancer Agency** -With renal impairment, the use of the following dosing intervals has been suggested: 24-36hrs for CrCl of 50-80ml/min, and 48hrs for CrCl of 10-50ml/min[23].	Clinical decision Consider increasing dosing interval as follows: CrCl of 50-80ml/min – 24-36hrs CrCl of 10-50ml/min – 48hrs
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)** – Significantly impaired renal function is a contra-indication. **Wyeth** – Renal clearance correlates with CrCl. Methotrexate t½ is inversely related to CrCl. **Kintzel et al**[4] - suggest for CrCl of 60ml/min; use 0.65 fraction of dose, for CrCl of 45ml/min, use 0.5 fraction of dose, for CrCl of 30ml/min, methotrexate is not recommended. **BC Cancer Agency** – suggested dose modification GFR; 61-80 give 75% dose; 51-60 =70%, 10-50 30-50%; <10 =CI **Renal Drug Handbook** - GFR >50ml/min use 100% dose; GFR 10-50ml/min use 50% dose; GFR<10ml/min – avoid. **Dialysis** **Bennett et al, 1999** - Give 50% dose[7]. **Renal Drug Handbook** - Contraindicated in CAPD. Dialysed in HD and HDF/High flux. Use 50% of the normal dose at least 12hrs before next dialysis. Use with caution. CAV/VVHD – use 50% of normal dose.	**CrCl (ml/min)** **Dose** >80 100% 60 65% 45 50% <30 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 conc^{n}, 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 on dose adjustment. Severe renal toxicity has occasionally been reported after treatment and renal function should be monitored before each course. **Fischer D et al**[23] suggest the following: For GFR 10-60ml/min, use 75% dose, for GFR <10ml/min, use 50% dose. **Renal Drug Handbook** – GFR >10ml/min use 100% dose GFR <10ml/min use 75% dose **Dialysis** **Renal Drug Handbook** – HD, CAPD and HDF/High flux dose as in GFR <10mls/min (75% dose). CAV/VVHD dose as in normal renal function.	**GFR (ml/min)** **Dose** >10 100% <10 75% Consider a dose reduction for high doses of mitomycin when GFR 10-60 ml/min. **Dialysis** – Haemodialysis and CAPD dose as in GFR <10mls/min (75% dose)
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 labs 2008) –** No experience in this group therefore use in caution in mild to moderate renal impairment and contraindicated in severe renal impairment. **BC Cancer agency** – Dose adjustment required but no details found**.**	Clinical decision – dose reductions required.
Mitoxantrone	Extensive metabolism in the liver. Excretion is predominantly bile and faeces. 5-10% of dose is excreted in the urine within 5 days.	**SPC (Wyeth 2008)** – No information **Wyeth** – Dose reductions appear to be unnecessary in patients with reduced renal function. The principal dose-limiting side effect is myelosuppression, which should be monitored. Mitoxantrone does not appear to be eliminated by haemodialysis and dose adjustments are not needed in such patients. **BC Cancer Agency** – No dose reduction required **Dialysis** Extensively tissue bound therefore unlikely to be eliminated by haemodialysis or peritoneal dialysis. Dose adjustments may not be needed in patients undergoing this procedure[13] **Dialysis** **Renal Drug Handbook** – HD, CAPD, HDF/High flux and CAV/VVHD – not dialysed, dose as in normal renal function	No dose reductions necessary.

Drug	Pharmacokinetics	Available Information	Recommendation
Oxaliplatin	In vitro, there is no evidence of cytochrome P450 metabolism. Extensive nonenzymatic 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)** – Oxaliplatin has not been studied in patients with severe renal impairment (<30ml/min). In patients with moderate renal impairment, treatment may be initiated at the normally recommended dose. Consider risk/benefit ratio. There is no need to dose reduce in patients with mild renal dysfunction. **Sanofi** – Massari C et al[24] looked at patients with normal and impaired (27-57ml/min) renal function. Data showed the same plasma levels between the 2 groups, and the clearance of both total and free platinum as well as AUC correlated with the CrCl. Toxicities were similar in the 2 groups. **Takimoto CH et al**[25] – Data found to support the recommendation that dose reductions of single-agent oxaliplatin are not necessary in patients with a CrCl greater than 20ml/min (dose based on 130mg/m^2 every three weeks). **BC Cancer Agency**- GFR >30ml/min 100%, < 30ml/min – No information. **Dialysis** **Sanofi** – It is not anticipated that dialysis treatment during oxaliplatin therapy would cause any problems.	Moderate renal impairment – treat at normal dose, and monitor renal function. Dose adjust according to toxicity. CrCl <20m/min –dose reduce **Dialysis** It is not anticipated that dialysis treatment during therapy would cause any problems.
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 (Abraxis Bioscience 2009)** – No recommendations **BMS** – within 24-48 hrs following administration, <10% of the dose appears in the urine. In dialysis patients, full dose has been given (on non-dialysis days) with a typical toxicity profile. **Dialysis** [26] - Paclitaxel chemotherapy is efficacious and feasible for patients undergoing haemodialysis (NB study was carried out in ovarian cancer at 150mg/m^2). **Bekele et al 2001-** reports a case of a patient that receives paclitaxel whilst on haemodialysis. The authors recommended dose reduction (135mg/m2) in dialysis patients [27]. **Renal Drug Handbook** – HD, CAPD, HDF/High flux and CAV/VVHD – Dose as in normal renal function **BC Cancer Agency** – No adjustment necessary	No dose reductions necessary. **Dialysis** – clinical decision
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**) – Results from a published study in 13 patients with impaired renal function suggested the following dosage adjustment. Dosage was adjusted to 75% at a CrCl of 40-59 ml/min (3 mg/m^2) and to 50% at a CrCl of 35-39 ml/min (2 mg/m^2). There are insufficient data to recommend a starting or a subsequent dose for patients with creatinine clearance < 35 ml/min. Given limited data, if CrCl <60 ml/min, pentostatin is contra-indicated.	**CrCl (ml/min)** / **Dose** >59 / 100% 40-59 / 75% 35-39 / 50% <35 / not recommended
Pemetrexed	Not metabolised to an appreciable extent. Mainly excreted (70-90%) unchanged in the urine.	**SPC (Eli Lilly 2009) –** Drug can be safely given if GFR>45mls/min, lower than this adjustments cannot be recommended. **Lilly –** Case report of a patient receiving grade 3-4 toxicity after administration with a GFR 19mls/min. **BC Cancer Agency -** GFR<45 delay treatment	GFR>45mls/min 100% dose Otherwise clinical decision May be hazardous in severe renal impairment.

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 2006)** – Caution advisable in patients with renal dysfunction. **Tricot et al 1996**[22] - With serum creatinine >177µmol/L, doses should be substantially reduced.	Lack of available information. If serum creatinine >177µmol/L, give 50% dose. For severe renal impairment – not recommended.
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[11]	**SPC (Astra Zeneca 2002)** – See recommendations **Renal Drug Handbook** – As guidelines. **Dialysis** **Renal Drug Handbook** – HD, CAPD, HDF/High flux and CAV/VVHD. Unlikely to be dialysed – avoid use.	**CrCl** ml/min **Dose** **Interval** >65 100% 3 wkly 55-65 75% 4 wkly 25-54 50% 4 wkly <25 0% -
Rituximab	Mean serum $t^{1}/_{2}$ increases with dose and repeated 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 information **BC Cancer Agency** – No dose reduction required.	Probably no dose reduction necessary.
Temozolomide	Temozolomide is rapidly and completely absorbed with 100% bioavailabiltiy. 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)** – No data in renal dysfunction. Analysis of population pharmacokinetic data revealed that plasma temozolomide clearance was independent of age and renal function. It is unlikely that dose reductions are required in patients with renal dysfunction. **BC Cancer agency** – No dose reduction required **Renal Drug Handbook** – Dose as in normal renal function. **Dialysis** **Renal Drug Handbook** – HD, CAPD, HDF/High flux and CAV/VVHD – Dose as in normal renal function..	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.	**SPC (Celgene 2008) –** Thalidomide Pharmion has not formally been studied in patients with impaired renal function. No specific dose recommendations for these patient populations are available. Patients with severe organ impairment should be carefully monitored for adverse reactions **Pharmion** – Doses in patients with renal impairment should be titrated with observed tolerance and toxicity and the highest tolerated dose should be selected. Since renal insufficiency is common among multiple myeloma patients, the recommended adult dosage has been established in populations of patients including those with renal impairment. **Renal Drug Handbook –** Dose as in normal renal function **BC Cancer Agency** – No dose reduction required **Dialysis** **Renal Drug Handbook** – HD, CAPD, HDF/High flux and CAV/VVHD – Dose as in normal renal function.	No dose reduction necessary.

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 or renal function. **BC cancer agency –** Dose adjustments recommended but no values.	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)** – No information. **Wyeth** – No information. **BC Cancer agency** – Adjustment required but no information.	Lack of information available. Consider dose reduction, but no formal recommendations.
Tipifarnib	Unknown	**Ortho Biotech –**No clinical studies have been conducted in this group of patients. A population pharmacokinetic analysis indicated that there was no relationship between tipifarnib clearance and creatinine clearance.	Clinical decision – unlikely to require a dose reduction.
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 the use of topotecan in patients with CrCl < 20 ml/min and topotecan is contra-indicated in this group of patients. Plasma clearance in patients with CrCl 41-60ml/min is decreased to ~67%. In moderate renal impairment, plasma clearance was reduced to ~34%. **Merck** – Dose-limiting toxicities, mainly neutropenia and thrombocytopenia are seen in patients with impaired renal function. In patients with moderate renal impairment, a starting dose of 0.75mg/m^2 is recommended. Further reductions are recommended in heavily pre-treated patients. **Kintzel et al**[4] suggest for CrCl of 60ml/min; use 0.8 fraction of dose, for CrCl of 45ml/min, use 0.75 fraction of dose, for CrCl of 30ml/min, use 0.7 fraction of dose. **BC Cancer Agency**-GFR 40-60ml/min =100% dose, 20-39= 50%, < 20 =not recommended. **Dialysis** Topotecan is effectively cleared by HD. Plasma clearance may be increased fourfold whilst on HD[28]. **Renal Drug Handbook** – CAV/VVHD – 0.5-0.75mg/m^2/day and monitor closely.	**CrCl (ml/min)** **Dose** >40 100% 20-39 50% <20 CI

Drug	Pharmacokinetics	Available Information	Recommendation
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 2009) –** 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 adjustments necessary. **Dialysis** **Renal Drug Handbook** – HD, CAPD, HDF/High flux and CAV/VVHD – Dose as in normal renal function.	Probably no dose reduction necessary.
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 208)** – No information. **Medac** – No information for GFR >30mls/min, If GFR<30ml/min reduce dose by approximately 40%.	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 Serono 2008)** – Use with caution in patients with renal impairment. There is no experience with the UFT/calcium folinate combination in patients with renal impairment. Physicians should exercise caution. **BMS** – The effect of renal impairment on the excretion of UFT has not been assessed. Although the primary route of elimination of UFT is not renal, caution should be exercised in patients with impaired renal function. Monitor closely.	Lack of information available. Probably no dose reduction necessary Monitor for toxicity.
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)** – No information. **Faulding** – No dose reduction necessary. **Renal Drug Handbook** – No dose reduction **BC Cancer Agency** – No dose adjustments necessary. **Dialysis** **Renal Drug Handbook** – HD, CAPD, HDF/High flux and CAV/VVHD – Dose as in normal renal function.	No dose reduction necessary
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)** – no information. **Lilly** – no dose reduction necessary. **Renal Drug Handbook –** no dose reduction required. **Dialysis** **Mayne -** Not dialysable *in vitro* but these results cannot be automatically transferred to an *in vivo* situation **Renal Drug Handbook** – HD, CAPD, HDF/High flux and CAV/VVHD – Dose as in normal renal function.	No dose reduction necessary

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)** – no information. **Lilly** – no dose reduction necessary. **BC Cancer Agency** – No dose adjustments necessary **Dialysis** **Renal Drug Handbook** – HD, CAPD, HDF/High flux and CAV/VVHD – Dose as in normal renal function.	No dose reduction necessary
Vinorelbine	Widely distributed in the body, mostly in spleen, liver, kidneys, lungs, thymus; moderately in heart, muscles; minimally in fat, brain, bone marrow. High levels found in both normal and malignant lung tissues, with slow diffusion out of tumour tissue. 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)** – There is no pharmacokinetic rationale for reducing vinorelbine dose in patients with impaired kidney function. **Pierre-Fabre** – Clearance is mainly hepatic. **Renal Drug Handbook** – No dose reduction. **BC Cancer Agency** – No dose adjustments necessary. **Dialysis** **BC Cancer Agency** - Reduction from 25 mg/m² to 12.5 mg/m² IV for one dose on day 1 weekly (given after hemodialysis) was reported in one patient. **Renal Drug Handbook** – HD, CAPD, HDF/High flux and CAV/VVHD – Dose as in normal renal function and monitor closely.	No dose reduction necessary

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