Chapter 12: Pharmacokinetics of Chemotherapeutic Agents in Kidney Disease

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INTRODUCTION

The liver and kidneys serve as the major pathways for drug metabolism and elimination, with much smaller contributions from the fecal and reticuloendothelial systems. As shown in Figure 1, some unique aspects of renal physiology that make the kidneys particularly susceptible to drug exposure and injury include 1) a high blood flow rate and therefore high drug delivery rate to the kidney (blood flow to the kidney approximates 25% of cardiac output); 2) the medulla's considerable concentrating ability, which enhances local drug tissue concentration; 3) the presence of organic anion transporters within the tubules, which allow nephrotoxic medications and their toxic metabolites to become concentrated within the tubules; and 4) the presence of renal enzymes, which can form toxic metabolites and reactive oxygen species (CYP450 and flavin-containing monooxygenase) (1,2).

Cancer drugs have been demonstrated to cause nephrotoxicity via direct tubular injury, tubular obstruction, injury to the tubulointerstitium, and glomerular damage. Certainly, the prevalence of renal insufficiency in cancer patients, and the kidney's role in drug metabolism, has implications for the choice and dosing of chemotherapeutic agents. In this section, recommendations for dose modifications for some of the more frequently used chemotherapeutic agents, which require adjustments in patients with various levels of CKD, will be discussed. For a more complete discussion of all chemotherapeutic agents that require renal dosing, the reader is referred elsewhere (3–6).

Published guidelines for dose modification of chemotherapy for cancer patients with CKD are largely based on limited pharmacokinetic (PK) and pharmacodynamic (PD) data and often on studies of poor quality (physician-initiated postmarketing studies, small sample sizes). Historically, the Cockcroft and Gault (CG) formula was most often used to estimate GFR, and this equation has been shown to overestimate GFR. Additionally, before the advent of the isotope dilution mass spectroscopy (IDMS) creatinine assay, the variability in creatinine assays likely affected the PK and PD data from past studies, and therefore, the resulting dosing recommendations being used currently (7). What remains largely unaddressed in all PK and PD studies to date is that CKD can significantly alter nonrenal clearance and modify bioavailability of drugs predominantly metabolized by the liver and intestine. It has been shown that CKD suppresses various liver metabolic enzymes (CPT2C9, CYP2C19, and CYP3A4), and these effects are clinically significant (8). GFR is the metric used to guide dose adjustment, and as shown in Table 1 a number of equations are available to calculate GFR. In cancer patients, compared with Tc99mDPTA clearance, the Martin and Wright formulae seem to have the best concordance, followed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (60.2%, 56.5%, and 56.3%, respectively). However, there were similar levels concordance in dosage selection between the assorted formulae and Tc99mDPTA clearance when selecting carboplatin dose (9), so the variations in concordance may not appreciably change final dose recommendations.

CARBOPLATIN

Notwithstanding all of these limitations, carboplatin is one of the few chemotherapeutic agents with good prospective PK and PD data in CKD patients (10–12). It is the third most commonly prescribed cytotoxic agent (3). About 70% of the administered dose is eliminated by the kidneys, and the drug has

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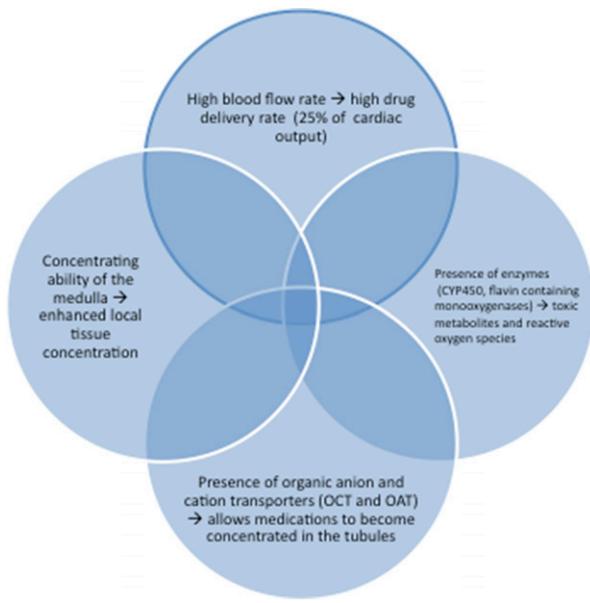
Figure 1. Susceptibility of the kidneys to drug exposure and delivery.

only rarely been associated with AKI at high doses (1,600–2,400 mg/m^2) following bone marrow transplant (BMT) (13,14). At the usual doses range from 400 to 600 mg/m^2, the drug is much less nephrotoxic. Neuropathy and myelosuppression are its main toxicities. Calvert's formula is used to calculate the area under the curve (AUC): carboplatin dose (mg) = target AUC × (GFR + 25).

The drug can be administered to hemodialysis (HD) patients to achieve an AUC of 4–6 such that carboplatin dose (mg)=Target AUCx25. The drug is not avidly protein bound shortly after administration, and approximately 70% is cleared by HD if performed within several hours after infusion (15). Importantly, a majority of carboplatin becomes protein bound after 24 hours (12), so carboplatin administration should be coordinated to perform dialysis within 24 hours of dosing (16).

CISPLATIN

Although they are members of the same chemical family, cisplatin is considered to be superior therapy for specific tumor types compared with carboplatin. Unfortunately, nephrotoxicity is the dose-limiting side effect of this very effective chemotherapeutic agent (17–19). In the earliest reports of renal toxicity, incidence rates of 28%–36% were reported in patients receiving a single dose of 50 mg/m^2 (Bristol Meyer Packaging), but the severity of renal toxicity decreased following institution of vigorous hydration protocols with normal saline (NS). The chloride in NS decreases the formation of toxic reactive platinum compounds (20). Initial declines in a GFR range from 12% to 19% (21–23), but some patients have shown improvement in renal function over time, implying that renal recovery is possible in some cases (23,24). However, there is usually persistent subclinical renal injury following cisplatin exposure (20).

A detailed understanding of the mechanisms by which cisplatin induces renal toxicity remains unclear. The kidney

Table 1. eGFR formulas in cancer patients

Equation	Considerations

Wright	Derived from an oncology population
	  -Population contained 66% females
	-In oncology studies:
	  -More accurate when the GFR greater than 50ml/min/1.73m2
	  -Tends to overestimate GFR when less than 50ml/min/1.73m2
	  -Less biased and more accurate than Jelliffe, CG, and MDRD when GFR greater than 50ml/min/1.73m2

Martin	-Derived from an oncology population -In oncology studies with mean GFR 85ml/min/1.73m2, less biased and more accurate than Jelliffe, CG, Wright and MDRD -No specific data on patients with GFR less than 50ml/min/1.73m2
Cockcroft-Gault	-Derived from male inpatients at a VA hospital -In oncology studies, tends to underestimate GFR
Jelliffe	-Derived from renal transplant patients -In oncology studies, tends to underestimate GFR

MDRD	-In oncology studies:
	  -Tends to underestimate GFR
	-In studies on non cancer populations:
	  -When GFR greater than 60 ml/min per 1.73 m², tends to underestimate GFR
	  -More accurate and less biased than CKD EPI when GFR less than 60 ml/min per 1.73 m²
	  -Is less accurate with near normal GFR, extremes of age and weight and amputation

CKD-EPI	In studies on non cancer populations: -More accurate and less biased than MDRD when GFR greater than 60ml/min/1.73m2

selectively accumulates cisplatin and its analogues to a greater extent than other organs(18). On microscopic examination, cisplatin produces a tubulointerstitial lesion, with acute tubular necrosis being the predominant lesion, whereas the glomeruli are spared (20,25). Cisplatin-induced tubular damage affects the PK of subsequent cisplatin doses and causes a decrease in the percentage of cisplatin excreted and an increase in the AUC following sequential doses of the drug (26,27).

The drug is 90% protein bound within 2 hours after infusion, and 30% is excreted in the urine within 24 hours. Dosing guidelines for patients with CKD are empiric. Kintzel recommends for a creatinine clearance (CrCl) of 46–60 mL/min, give 75% of the usual dose; for a CrCl of 31–45 mL/min, give 50% of the usual dose, and for a CrCl <30 mL/min, the drug is not recommended (4). Arnoff recommends for CrCl of 10–50 mL/min, give 75% of the usual dose, and for CrCl <10 mL/min, give 50% of the usual dose. The manufacturer recommends withholding repeat administration of the drug until the serum creatinine concentration is <1.5 mg/dL. Cisplatin has been successfully administered to HD patients with similar tolerance as in patients with normal renal function. Because the drug is highly and irreversibly protein bound and because free cisplatin is well dialyzed, drug that is dialyzed off cannot be replaced by bound drug. As such, cisplatin must be given on a nondialysis day. For HD patients, it is recommended that the initial dose be reduced by 50%, or 25–50 mg/m^2 every 3–6 weeks (16).

IFOSFAMIDE

Although hemorrhagic cystitis is the predominant toxicity of this alkylating agent, renal toxicity can be dose limiting. A number of histopathologic changes in the kidney have been observed with ifosfamide and include segmental glomerular sclerosis, tubulointerstitial nephritis, tubular atrophy, and interstitial fibrosis (28). Chloroacetaldehyde, a metabolite of ifosfamide, is toxic to renal epithelial cells and may contribute to nephrotoxicity of the parent drug (29,30). Clinical manifestations of renal tubular toxicity include Fanconi syndrome, proximal and distal renal tubular acidosis, hypophosphatemia, hypokalemia, and nephrogenic diabetes insipidus.

Up to 87% of ifosfamide and its metabolites are recovered in the urine, and up to 41% of the dose is recovered in the urine as alkylating activity (31). Central nervous system (CNS) toxicity may be linked to the accumulation of the metabolite chloroacetaldehyde, and the risk of CNS toxicity is greater in patients with abnormal renal function (32). Dosing guidelines are empiric and vary widely. Kintzel recommends for CrCl of 46–60 mL/min, give 80% of dose; for CrCl of 31–45 mL/min, give 75% of dose; and for CrCl of <30 mL/min, give 70% of dose. Aronoff recommends giving 75% of the usual dose for a GFR <10 mL/min (4,5). The drug has been used without significant myelosuppression or neurotoxicity in anuric and oliguric patients on HD at starting doses of 1.5 g/m^2 at 48- to 72-hour intervals, with HD to

follow in the range of 3–14 hours after drug administration. Subsequent dose adjustments were based on signs of neurotoxicity or myelosuppression (33). For HD patients with urine output, hydration and Mesna are needed to prevent hemorrhagic cystitis, and a hydration protocol is outlined elsewhere (33,34).

CYCLOPHOSPHAMIDE

There are no clear guidelines for dose adjustment of cyclophosphamide in the setting of renal insufficiency. Although cyclophosphamide is largely cleared by hepatic metabolism, up to 60% of the total dose is eliminated by the kidney as the parent drug or metabolites (35), and renal insufficiency is associated in changes in the PK profile of the parent drug and its metabolites. Aronoff recommends giving 75% of the usual dose for GFR <10 mL/min. Because the AUC of cyclophosphamide is increased in HD patients, it is recommended that the dose be reduced by 25% in this group (36,37). The drug should be given after HD because the drug and its metabolites are dialyzable.

METHOTREXATE (MTX)

Renal excretion of this antifolate agent is 60% and 94% when the drug is administered over 6 and 24 hours, respectively. Nephrotoxicity has been observed at doses exceeding 1 g/m^2 (38) and results from intratubular precipitation of MTX and its metabolites in the distal tubules, which causes an obstructive tubulopathy and decreased glomerular filtration (4,39). Pretreatment with cisplatin has been reported to increase MTX toxicity, possibly by decreasing renal clearance (40). AKI prolongs extrarenal toxicity (myelosuppression and gastrointestinal toxicity) and is observed at plasma concentrations 5–20 μmol/L at 24 hours, 0.5–2 μmol/L at 48 hours, and 0.05–0.1 μmol/L at 72 hours following drug administration. When serum drug levels reach toxic levels, intravenous leucovorin is generally used to circumvent MTX's inhibition of dihydrofolate reductase to "rescue" normal cells from MTX (38).

MTX is poorly soluble in acid urine, and decreased flow rates increase its concentration in the renal tubules. Prevention remains the best treatment for MTX toxicity and includes measures to alkalinize and maximally dilute the urine with bicarbonate containing intravenous fluids as needed to achieve a urine pH > 7.0 and a urine output of ≥150 mL/h. Because the drug is not lipophilic, it accumulates at high concentrations in ascites and pleural fluid, which can prolong drug elimination and toxicity, especially in the setting of AKI. Consequently, it is recommended that fluid collections be drained prior to high-dose MTX.

When AKI occurs, it is reversible in 70%–100% of cases with conservative medical management (38), and the drug can be

readministered following recovery of renal function. In cases where dialysis requiring AKI occurs and is associated with prolonged myelosuppression and/or gastrointestinal (GI) ulceration, carboxypeptidase-G(2) can be obtained on a compassionate, albeit expensive basis, for management of severe MTX intoxication (41–43). Carboxypeptidase-G(2) rapidly hydrolyzes MTX into its inactive metabolites and decreases median MTX concentrations by 98.7%.

Kintzel recommends for CrCl of 46–60 mL/min, give 65% of dose; for CrCl of 31–45 mL/min, give 50% of dose, and for CrCl <30 mL/min, do not administer. Aronoff recommends a dose reduction of 50% with a CrCl of >10–50 mL/min and avoiding the drug for CrCl of <10 mL/min (4,5). Although the drug is removed by high-flux HD and charcoal hemoperfusion, because it is 50% protein bound, there is postdialysis rebound in MTX concentrations of 90%–100% of the preprocedure levels. Therefore, patients may require daily or continuous renal replacement therapy to avoid rebound toxicity.

PEMETREXED

Pemetrexed is a derivative of MTX, and up to 90% of the drug is excreted unchanged in the urine. The drug has been associated with acute tubular necrosis and interstitial fibrosis (44,45). The manufacturer recommends avoiding the drug for a CrCl of <45 mL/min and avoiding nonsteroidal anti-inflammatory medications in the days before and after pemetrexed dosing in patients with a CrCl of 45–79 mL/min (46). When nephrotoxicity occurs, it is probably best to avoid re-exposure.

MELPHALAN

Melphalan is effective therapy for multiple myeloma (MM) and amyloidosis. Urinary excretion of melphalan ranges from 10% to 34%, and the AUC for melphalan is inversely correlated with the GFR (47). Bone marrow suppression, the limiting side effect of melphalan, increases when the drug is given in CKD patients (48). Kintzel recommends for CrCl of 46–60 mL/min, give 85% of dose; for CrCl of 31–45 mL/min, give 75% of dose; and for CrCl of <30 mL/min, give 70% of dose. Aronoff recommends giving 75% of the dose for a CrCl of >10–50 mL/min and 50% for those with a CrCl of <10 mL/min (4,5). Patients on dialysis have been safely and successfully treated with melphalan prior to stem cell transplant at doses between 60 and 140 mg/m^2 (49,50).

LENALIDOMIDE

Lenalidomide is a thalidomide analogue used to treat multiple myeloma (MM) and myelodysplastic syndrome (MDS). Eighty-two percent of the drug is excreted unchanged in the urine, and the AUC and risk for drug toxicity are increased in CKD patients (51,52). Rare cases of AKI due to acute and chronic interstitial nephritis (AIN) have been reported with lenalidomide (53–55). For MDS, the manufacturer recommends 5 mg daily for CrCl of <59 mL/min, and increasing the dosing interval to every 48 hours for CrCl of <30 mL/min. For patients on HD, a dose of 5 mg should be given three times a week following each hemodialysis. For MM, the manufacturer recommends a 10-mg daily dose for CrCl of >30–59 mL/min, a 15-mg dose every 48 hours for CrCl of <30 mL/min, and 5 mg daily for HD patients to be given after HD on dialysis days (56).

CYTARABINE

Cytarabine is an antimetabolite that is extensively converted to uridine-arabinoside (Ara-U), and 10%–30% of the parent drug and 85% of the inactive metabolite are eliminated by the kidneys (57). High-dose cytarabine (HDAC) can produce significant and sometimes irreversible neurotoxicity. Renal dysfunction is an independent risk factor for cerebellar (dysarthria, nystagmus, gait ataxia, dysdiadochokinesia) and noncerebellar (somnolence, seizures) neurotoxicity. The inactive metabolite Ara-U inhibits cytidine deaminase activity, and in the setting of renal dysfunction, further delays cytarabine clearance and increases serum and cerebral spinal fluid levels of the parent drug (58). For patients with CKD receiving HDAC, Kintzel recommends for CrCl of 46–60 mL/min, give 60% of the dose; for CrCl of 31–45 mL/min, give 50% of the dose; and for CrCl of <30 mL/min, do not administer (4). Smith developed a dosing algorithm for HDAC based on daily serum creatinine measurements while the patients were on therapy. If the patient's baseline serum creatinine concentration was between 1.5 and 1.9 mg/day, or if baseline serum creatinine level increased by 0.5–1.2 mg/dL during treatment, then the dose of Ara-C was reduced to 1 g/m^2 per dose. If the serum creatinine level was >2 or the change was >1.2 mg/dL, then the dose of Ara-C was reduced to 0.1 g/m^2/day (standard dose) as a continuous infusion. (59). Cytarabine and Ara-U are both cleared by HD. There are a few case reports of patients on HD who have tolerated treatment with standard doses cytarabine (continuous infusion, 100 mg/m^2 per day) when HD was performed on day 1 of cytarabine infusion and then every other day. In one case, HD was performed consecutively on days 1 and 2 as well (60,61). HDAC has been safely used in a patient with lymphoma on hemodialysis. The patient received two doses of HDAC 1 g/m^2, 24 hours apart, was dialyzed 6 hours after each dose, and then resumed his usual dialysis schedule (62).

CAPECITABINE

Capecitabine is a pyrimidine analogue that is preferentially converted to 5-fluorouracil (5-FU) within tumor cells.

Although neither capecitabine nor 5-FU is renally cleared, in patients with CKD, there is retention of active metabolites and a resultant increase in systemic toxicity (63). The manufacturer recommends a dose reduction of 75% from the starting dose of 1,250 mg/m^2 for patients with a CrCl between 30 and 50 mL/min, and for patients with a CrCl of <30 mL/min, it is recommended that capecitabine be discontinued (64). With careful monitoring and dose reduction, the drug has been effectively and safely used in patients with advanced CKD (GFR < 30 mL/min) and patients on hemodialysis (65).

BLEOMYCIN

Bleomycin is not nephrotoxic, but urinary excretion accounts for close to 70% of the intravenous dose of bleomycin (66,67), and patients with renal dysfunction appeared to be at higher risk for bleomycin pulmonary toxicity, the major dose-limiting toxicity of this drug (48,68). Kintzel recommends for CrCl of 46–60 mL/min, give 70% of dose; for CrCl of 31–45 mL/min, give 60% of dose; and for CrCl of <30 mL/min, avoid the drug. Aronoff recommends giving 75% of the dose for CrCl of >10–50 mL/min and 50% for those with a CrCl of <10 mL/min (4,5). Because pulmonary toxicity can be cumulative in patients with CKD, if bleomycin is administered to patients with CKD, repeat pulmonary function tests prior to each drug administration may be prudent.

MOLECULARLY TARGETED AGENTS

Vascular endothelial growth factor (VEGF) pathway inhibitors (bevacizumab), tyrosine kinase inhibitors (sorafenib, nilotinib, and dasatinib), and epithelial growth factor receptor (EGFR) pathway inhibitors (erlotinib) have been described to cause nephrotoxicity. Observed renal toxicities among these relatively new agents include acute tubular necrosis, proteinuria, hypertension, thrombotic microangiopathy, acute interstitial nephritis, tumor lysis syndrome, and glomerulonephritis (69–71).

Bevacizumab
As per the manufacturer's guidelines, no studies were done to investigate the PK of bevacizumab in patients with CKD. For patients with a CrCl between 20 and 39 mL/min, the manufacturer recommends a 50% decrease in the usual starting dose with increases in subsequent doses as tolerated, but no >400 mg. For patients with a CrCl of 40–59 mL/min, doses >600 mg are not recommended (72). There is only one report on the PK of bevacizumab in a dialysis-dependent patient with metastatic renal cancer who received 5 mg/kg every 2 weeks. The drug was not dialyzable, and its pharmacokinetic parameters were similar to the reference values of patients with normal renal function. The drug can be administered any time before or after hemodialysis (73).

Tyrosine kinase inhibitors
Erlotinib
The PK of erlotinib were never studied in patients with renal insufficiency. There are case reports of patients with CrCl between 25 and 41 mL/min who tolerated the usual dose of 150 mg/day without significant toxicity (74). There are no data on its use in hemodialysis patients.

Imatinib
Although there is no significant renal excretion, the manufacturer recommends that patients with a CrCl of 20–30 mL/min receive 50% of the starting dose, with dose escalation as tolerated but not to exceed 400 mg/day. For those with CrCl of 40–59 mL/min, doses >600 mg are not recommended. Imatinib exposure can increase up to two-fold in patients even with mild renal impairment (CrCl < 60 mL/min) and that there is a significant correlation between decreased renal function and the incidence of serious adverse events (75). PK data on one patient with ESRD on dialysis that received 400 mg/day indicates that imatinib and its metabolite are unchanged in patients with ESRD on hemodialysis (74).

Lenvatinib
The package insert recommends a dose reduction to 14 mg daily for patients with CrCl is <30 mL/min. There are no data on the use of lenvatinib in patients on hemodialysis.

Sunitinib
Sunitinib use was studied in two ESRD patients. The PK parameters of sunitinib and its major metabolite were similar in patients on HD and those with normal renal function. Furthermore, sunitinib is nondialyzable. Doses of 50 mg/day for 4 weeks every 6 weeks were well tolerated (76).

Sorafenib
Although the manufacturer does not recommend any dose adjustment for patients with any level of renal insufficiency (77), based on dose-limiting toxicity in a phase 1 study, a starting dose of 200 mg twice a day for CrCl of 20–39 mL/min and 200 mg once daily for patients on hemodialysis was recommended. No recommendations could be made for those with a CrCl <20 mL/min and not on dialysis (78).

Vandetanib
The manufacturer recommends that the starting dose should be reduced to 200 mg in patients with a CrCl of <50 mL/min (79). There are no data on use of this drug in hemodialysis patients.

BISPHOSPHONATES

Bisphosphonates are frequently administered to cancer patients for management of hypercalcemia of malignancy and osteolytic bone lesions. Zoledronic acid has been associated with acute tubular necrosis, especially after repeated dosing.

Table 2. Recommended dose adjustments for selected chemotherapies for patients with CKD and ESRD on HD

Drug	Creatinine Clearance (ml/min)						Hemodialysis
Carboplatin	Calvert Formula to calculate AUC						Calvert Formula with GFR=0 to achieve AUC 4-6
	Carboplain dose (mg)= Target AUCx(GFR+25)						Perform HD within 24 hours of dosing
	Aronoff			Kintzel			
	(% dose reduction from usual dose)						
	<10	10-50	>50	≤30	31-45	46-59	
Bleomycin	50%	75%	100%	Not recommended	60%	70%	
Cisplatin	50%	75%	100%	Not recommended	50%	75%	Reduce 50%, or 25-50mg/m2 every 3-6 weeks. Give on non HD days
Cyclophosphamide	75%	100%	100%				Reduce dose 25%. Give drug after HD.
Cytarabine	100%	100%	100%	Not recommended	50%	60%	
Ifosfamide	75%	100%	100%	70%	75%	80%	Starting doses of 1.5gm/m2 at 48-72hour intervals. HD 3-14 hours after administration.
Melphalan	50%	75%	100%	70%	75%	85%	Used at dose of 60mg/m2 with TBI with HD 24 and 72 hours after admininstration. At 140mg/m2 alone with HD 24-28 hours after administration.
Methotrexate	Avoid	50%	100%	Not recommended	50%	65%	Patients may require daily or continuous dialysis to treat drug toxicity.
Bevacizumab				For CrCl 20-39ml/min, decrease dose 50%	--For CrCl 40-59ml/min doses >600 not recommended		Can be administered any time with HD.
Capecitabine				Avoid	For GFR 30-50: Reduce by 75%		Consider 50% dose reduction and adjust based on observed side effects. HD per routine.
Imatinib				For CrCl 20-30ml/min decrease dose 50%. Do not exceed 400mg/day	For CrCl 40-59ml/min, avoid doses >600mg/day		
Lenalidomide				For MDS: 5mg daily. For MM, 15mg Q48hours	For MDS, 5mg Q48hours. For MM 15mg Q48hours	5mg 3xweek following each HD	
Levatinib				reduce to 14mg/day			
Pemetrexed				Avoid when CrCl <45ml/min			
Sorafenib				For CrCl 20-39ml/min start at 200mg 2xday			200mg 1xday

Although pamidronate is more notoriously associated with collapsing glomerulopathy, there are case reports of acute tubular necrosis with this agent as well (80). Dehydration, concomitant use of nephrotoxic medication, and overly frequent dosing of the bisphosphonates all increase susceptibility to deterioration of renal function following bisphosphonate exposure. The American Society of Clinical Oncology (ASCO) recommends that his zoledronate be avoided in patients with CrCl of <30 mL/min and that the initial dose of 4 mg be reduced to 3.5 mg for CrCl of 50–60 mL/min; 3.3 mg for CrCl of 40–49 mL/min; and 3 mg for CrCl of 30–39 mL/min. For pamidronate, the usual dose of 90 mg over 2–3 hours and ASCO recommends giving 90 mg over 4–6 hours for CrCl of <59 mL/min. Neither agent should be used more frequently than every 3–4 weeks, the serum creatinine should be checked prior to each administration, and the medication should be held if the creatinine increases >0.5 mg/dL with normal renal function or >1 mg/dL if there is abnormal renal function at baseline (81).

Table 2 includes commonly used chemotherapeutic drugs and their dose adjustment in the setting of CKD.

CONCLUSIONS

In summary, although the kidneys are a major pathway for drug metabolism, unfortunately, the quality of PK and PD data on commonly prescribed chemotherapeutic agents for CKD patients requiring chemotherapy is quite poor. This chapter was an effort to summarize the data that are available and to provide the treating physician with some guidance when treating patients with cancer and CKD.

TAKE HOME POINTS

- The liver and the kidneys serve the major pathways of drug metabolism and elimination with much smaller contributions from the fecal and reticuloendothelial systems.
- Published guidelines for dose modification of chemotherapy for cancer patients, with the exception of carboplatin, are largely based on limited pharmacokinetic and pharmacodynamic data.
- In several cases, the parent drug and its metabolites are responsible for systemic toxicity, and the presence of renal insufficiency can potentiate toxicity of the parent drug and its metabolites.

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REVIEW QUESTIONS

1. What is the best option for management of a patient on cisplatin who has lost approximately 50% of the GFR following the first three cycles?

    a. Continue cisplatin at the present dose
    b. Continue cisplatin at a reduced dose
    c. Consider alternative therapies

    Answer: c is correct. Patients can have episodes of AKI following each dose of *cis*-platinum. With each subsequent episode of AKI, the baseline serum creatinine may not return to its pretreatment value. Up to 30% of patients may have residual renal insufficiency due to *cis*-platinum nephrotoxicity. In this patient who has lost about 50% of his GFR following his initial treatment, cisplatin is not recommended, and it may be best to consider alternative therapies.

2. What is the dose of zoledronic acid recommended by American Society of Clinical Oncology for the administration to patients with CrCl of 30–39 mL/min?

    a. 4 mg
    b. 3.5 mg
    c. 3 mg
    d. Do not administer

    Answer: c is correct. The American Society of Clinical Oncology recommends that zoledronate should be avoided in patients with CrCl of <30 mL/min and that the initial dose of 4 mg be reduced to 3.5 mg for CrCl of 50–60 mL/min; 3.3 mg for CrCl of 40–49 mL/min; and 3 mg for CrCl of 30–39 mL/min.

3. What is the appropriate timing of cisplatin administration in an ESRD patient receiving hemodialysis?

    a. 2 hours prior to hemodialysis
    b. 6 hours prior to hemodialysis
    c. 12 hours prior to hemodialysis
    d. On the off-dialysis day

    Answer: d is correct. Because the drug is highly and irreversibly protein bound and because free cisplatin is well dialyzed, drug that is removed by dialysis cannot be replaced by bound drug. As such, cisplatin must be given on a nondialysis day.