

Systemic Treatments for Lung Cancer Patients Receiving Hemodialysis

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Authors' disclosures of conflicts of interest are found at the end of this article.

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Abstract

Chemotherapy, and now targeted therapies and immunotherapies, are widely used for the management of patients with all stages of lung cancer. Some challenges present when patients are receiving concomitant hemodialysis for various comorbid conditions. However, this should not immediately rule out a patient for treatment. Many drugs may be safely given to patients who are receiving hemodialysis with the proper dosing schedule and careful monitoring. This article will outline the current literature surrounding the use of these drugs in patients undergoing active hemodialysis while being treated for lung cancer.

Metastatic lung cancer is the leading cause of cancer death in the United States. These patients often have several comorbidities given their risk factors for developing lung cancer. Managing lung cancer patients with severe renal impairment or end-stage renal disease requiring hemodialysis (HD) remains a significant clinical challenge. Chemotherapy, immunotherapy, and targeted therapy can at times be given as treatment with careful consideration of pharmacokinetics and pharmacodynamics properties.

CHEMOTHERAPY

Platinum Drugs

Platinum drugs make up the cornerstone of many solid tumor chemo-

therapy regimens (Table 1). These agents crosslink strands of DNA, leading to antimetabolic effects from the inability of DNA to be repaired and further replicated. Appropriate dosing of platinum agents is critical as these drugs can cause numerous adverse effects. Multiple case studies exist pertaining to the effect of HD on cisplatin and carboplatin in lung cancer.

Cisplatin: Cisplatin is eliminated primarily by the kidneys (Bristol-Myers Squibb, 2010a). Administering cisplatin in HD patients requires dose adjustments in order to prevent toxicities associated with cisplatin separate from the nephrotoxicity. Also, timing of the cisplatin with HD must be considered. Since patients are already on HD, nephrotoxicity is not the major concern and intrave-

Table 1. Chemotherapy for Lung Cancer

Medication	Indication	Dose	Pharmacodynamics
Cisplatin	<ul style="list-style-type: none"> • NSCLC • SCLC limited and extensive stage 	<ul style="list-style-type: none"> • NSCLC: 75–100 mg/m² • SCLC limited stage: 60 mg/m²; • SCLC extensive stage: 80 mg/m² 	<ul style="list-style-type: none"> • Metabolism: inactivated by sulfhydryl groups in the bloodstream and cells • Excretion: urine (> 90%); feces (minimal)
Carboplatin	<ul style="list-style-type: none"> • NSCLC • SCLC 	<ul style="list-style-type: none"> • NSCLC: AUC 2–6 • SCLC: AUC 5–6 	<ul style="list-style-type: none"> • Metabolism: hepatic (minimal) to aquated and hydroxylated compounds • Excretion: urine (70% as carboplatin; 3%–5% as platinum)
Docetaxel	<ul style="list-style-type: none"> • NSCLC • SCLC 	<ul style="list-style-type: none"> • NSCLC: 75–100 mg/m² • SCLC: 100 mg/m² 	<ul style="list-style-type: none"> • Metabolism: hepatic via oxidation by CYP3A4 • Excretion: feces (~75%); urine (~6%)
Etoposide	<ul style="list-style-type: none"> • NSCLC • SCLC 	<ul style="list-style-type: none"> • NSCLC: 50–100 mg/m² • SCLC: IV 35–120 mg/m²; po 100–200 mg/m²/day 	<ul style="list-style-type: none"> • Metabolism: hepatic via CYP3A4 and 3A5, prostaglandin synthases, glutathione, and glucuronide conjugation • Excretion: urine (~56%); feces (44%)
Gemcitabine	<ul style="list-style-type: none"> • NSCLC • SCLC 	<ul style="list-style-type: none"> • NSCLC: 1,000–1,250 mg/m² • SCLC: 1000–1250 mg/m² 	<ul style="list-style-type: none"> • Metabolism: metabolized intracellularly by nucleoside kinases to the active diphosphate and triphosphate nucleoside metabolites • Excretion: urine (inactive metabolite ~92%–98%); feces (< 1%)
Irinotecan	<ul style="list-style-type: none"> • NSCLC • SCLC 	<ul style="list-style-type: none"> • NSCLC: 60 mg/m² • SCLC: 60–175 mg/m² 	<ul style="list-style-type: none"> • Metabolism: primarily hepatic by carboxylesterase enzymes; may also undergo CYP3A4 metabolism • Excretion: urine (> 90%); feces (minimal)
Paclitaxel	<ul style="list-style-type: none"> • NSCLC • SCLC 	<ul style="list-style-type: none"> • NSCLC: 135 mg/m² • SCLC: 80–175 mg/m² 	<ul style="list-style-type: none"> • Metabolism: hepatic via CYP2C8 and 3A4 • Excretion: feces (~71%); urine (~14%)
Nab-paclitaxel	<ul style="list-style-type: none"> • NSCLC 	<ul style="list-style-type: none"> • NSCLC: 100 mg/m² 	<ul style="list-style-type: none"> • Metabolism: hepatic via CYP2C8 (major) and CYP3A4 (minor) • Excretion: feces (20%); urine (4%)
Pemetrexed	<ul style="list-style-type: none"> • NSCLC, nonsquamous 	<ul style="list-style-type: none"> • NSCLC: 500 mg/m² 	<ul style="list-style-type: none"> • Metabolism: minimal • Excretion: urine (70%–90%)
Temozolomide	<ul style="list-style-type: none"> • NSCLC • SCLC 	<ul style="list-style-type: none"> • NSCLC: 75 mg/m²/day • SCLC: 75 mg/m² 	<ul style="list-style-type: none"> • Metabolism: hydrolyzed to active MTIC • Excretion: urine (~38%; parent drug 6%); feces (< 1%)
Topotecan	<ul style="list-style-type: none"> • SCLC relapsed 	<ul style="list-style-type: none"> • SCLC: IV 1.5 mg/m²/day; po 2.3 mg/m²/day 	<ul style="list-style-type: none"> • Metabolism: pH-dependent hydrolysis • Excretion: IV: urine (51%), feces (18%); po: urine (20%), feces (33%)
Vinorelbine	<ul style="list-style-type: none"> • NSCLC 	<ul style="list-style-type: none"> • NSCLC: 25–30 mg/m² 	<ul style="list-style-type: none"> • Metabolism: hepatic via CYP3A4 • Excretion: feces (46%); urine (18%)

Note. NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer; AUC = area under the curve; CYP = cytochrome P450; IV = intravenous; po = orally.

nous (IV) fluids should not be added to the regimen as they routinely are included for non-HD patients. Table 2 summarizes several case studies in the literature evaluating the dosing of cisplatin in end-stage renal disease (ESRD) patients.

There is a general consensus among case studies to reduce the cisplatin dose by 50%; however, the timing of the HD varies. Hemodialysis primarily removes only the free cisplatin. This free cisplatin is generally not replaced by the plasma-

bound cisplatin, so administration of the cisplatin can occur following HD or on non-HD days (Janus, Thariat, Boulanger, Deray, & Launay-Vacher, 2010). Removing the free cisplatin via HD directly after infusion may be counterintuitive as most of the free cisplatin would then be removed, potentially lessening the cytotoxic effect and possible antitumor activity. A case study involving an accidental overdose in a lymphoma patient with 750 mg of cisplatin showed HD is ineffective in remov-

Table 2. Chemotherapy Dose Adjustments in Hemodialysis

Medication	Package insert recommendation	Literature recommendations
Cisplatin ^a	<ul style="list-style-type: none"> PI does not recommend using in dialysis; contraindicated 	<ul style="list-style-type: none"> Administer 50% of dose post hemodialysis <ul style="list-style-type: none"> » Partially cleared by HD » Doses up to 80 mg/m² tolerated » Highly and irreversibly bound to plasma proteins » Free cisplatin is dialyzable; however, loss of free cisplatin does not affect already bound cisplatin » Administer 12-24 hours before HD sessions Administer 50% of dose if on continuous ambulatory peritoneal dialysis Administer 75% of dose if on continuous renal replacement therapy
Carboplatin ^b	<ul style="list-style-type: none"> No manufacturer recommendations for CrCl ≤ 15 mL/min 	<ul style="list-style-type: none"> Administer 50% of usual dose post hemodialysis <ul style="list-style-type: none"> » Dialyzable » Administer carboplatin after HD session when GFR is approximately equal to 0 to enter into the Calvert equation » Carboplatin is removed by HD; administer on a nondialysis day and perform HD 12-24 hours later Administer 25% of usual dose on CAPD Administer 200 mg/m² on CRRT
Docetaxel ^c	<ul style="list-style-type: none"> Renal excretion is minimal (~6%) so dose adjustment in renal dysfunction is unlikely 	<ul style="list-style-type: none"> Docetaxel is not dialyzed <ul style="list-style-type: none"> » Rapid half-life of 4 minutes » Rapidly bound to plasma proteins » PK data are unaffected, with no difference in plasma concentrations when compared to patients with normal renal function » Can give before or after HD No effect of CAPD on PK of docetaxel
Etoposide ^d	<ul style="list-style-type: none"> No data available from package labeling 	<ul style="list-style-type: none"> Administer 50% of usual dose before or after HD <ul style="list-style-type: none"> » PK parameters similar to that for normal renal function patients. Dose escalation recommended. » Not removed by HD » Efficacy maintained, but monitor closely for hematologic toxicity Peritoneal dialysis: administer 50% of dose; post-HD dose not necessary CRRT: Administer 75% of dose
Gemcitabine ^e	<ul style="list-style-type: none"> No dose adjustments based on manufacturer labeling; use with caution in preexisting renal dysfunction Discontinue if severe renal toxicity or hemolytic uremic syndrome during gemcitabine treatment 	<ul style="list-style-type: none"> Initial dose reduction recommended (20%-40% reduction) Rapidly deaminated after administration to inactive metabolite dFdU (< 10% parent drug eliminated via urine) Found to be safe in HD on days without HD 90% of dFdU is eliminated by urine and can be delayed (5- to 10-fold prolongation in elimination half-life) Unknown if gemcitabine is removed by HD, but dFdU is removed by HD Recommended to start HD 6-12 hours after gemcitabine administration
Irinotecan ^f	<ul style="list-style-type: none"> Use in HD not recommended by the manufacturer 	<ul style="list-style-type: none"> Reduce weekly dose from 125 mg/m² to 50 mg/m² and administer after hemodialysis or on nondialysis days <ul style="list-style-type: none"> » Even with dose reductions, reports of neutropenia (grades 1-4) reported » If tolerated, may increase dose to 80 mg/m² » Not dialyzable » SN-38 is significantly delayed in renal failure and partially dialyzable (up to 50%) <ul style="list-style-type: none"> - Uremic toxins may inhibit OATP1B1, delaying SN-38 transportation from the hepatocyte

Table 2. Chemotherapy Dose Adjustments in Hemodialysis (cont.)

Medication	Package insert recommendation	Literature recommendations
Paclitaxel ^a	<ul style="list-style-type: none"> No dosage adjustments provided in the manufacturer labeling Not dialyzable; used before or after hemodialysis 	<ul style="list-style-type: none"> Extensively metabolized by CYP and excreted mainly in bile Paclitaxel PK in HD patients is comparable to that for patients with normal renal function Studied primarily in the gynecology/oncology population
Nab-paclitaxel ^b	<ul style="list-style-type: none"> Not studied 	<ul style="list-style-type: none"> No available information Not dialyzable; use before or after hemodialysis
Pemetrexed ^c	<ul style="list-style-type: none"> Not recommended 	<ul style="list-style-type: none"> Not dialyzable Contraindicated in eGFR < 45 mL/min Retrospective evaluation of pemetrexed-induced renal injury, all with eGFR > 45 mL/min, was associated with severe myelosuppression and hospitalization If pemetrexed is to be used in renal dysfunction, all risk factors for AKI should be corrected One case of NSCLC with eGFR 25–55 mL/min <ul style="list-style-type: none"> » Four cycles of carboplatin and pemetrexed administered, then maintenance of pemetrexed of 500 mg/m² every 3 weeks. At dose 14 dose reduced to 400 mg/m², at dose 16 interval extended to q4wk; received 51 total doses of pemetrexed
Temozolomide ^d	<ul style="list-style-type: none"> Not studied 	<ul style="list-style-type: none"> The need for dose adjustment and dialyzability unknown Patients with mild to moderate renal dysfunction have similar PK compared to normal renal function; severe renal dysfunction has not been studied
Topotecan ^e	<ul style="list-style-type: none"> IV: avoid use in HD and CAPD; CRRT: administer 0.75 mg/m² po: CrCl < 30 mL/min reduce dose to 0.6 mg/m²/day and may increase by 0.4 g/m²/day if no severe hematologic or GI toxicities occur 	<ul style="list-style-type: none"> IV topotecan is dialyzable, with one case reporting 60% removal with HD Administer on non-HD days or after HD A relationship between topotecan exposure (AUC) and myelotoxicity cannot be inferred
Vinorelbine ^f	<ul style="list-style-type: none"> No dosage adjustments provided in the manufacturer labeling 	<ul style="list-style-type: none"> Recommend initial dose reduction to 20 mg/m²/wk due to neutropenia seen with 25 mg/m²/wk No data of oral vinorelbine Removal by HD not studied; recommended to give after HD sessions or on nondialysis days

Note. PI = package insert; HD = hemodialysis; CrCl = creatinine clearance; GFR = glomerular filtration rate; CAPD = continuous ambulatory peritoneal dialysis; CRRT = continuous renal replacement therapy; PK = pharmacokinetic; dFdU = 2',2'-difluorodeoxyuridine; CYP = cytochrome P450; eGFR = estimated GFR; AKI = acute kidney injury; IV = intravenous; AUC = area under the curve; po = orally; GI = gastrointestinal.

^aBristol-Myers Squibb (2010a); Charlier, Kintz, Dubois, & Plomteux (2004); Janus, Thariat, Boulanger, Deray, & Launay-Vacher (2010); Watanabe et al. (2003).

^bBristol-Myers Squibb (2010b); Fong, Fetterly, McDougald, & Iyer (2014); Inoue et al. (2004); Janus et al. (2010); Takezawa, Okamoto, Fukuoka, & Nakagawa (2008); Tanaka (2015).

^cHochegger, Lhotta, Mayer, Czejka, & Hilbe (2007); Janus et al. (2010); Kaneda, Okamoto, & Nakagawa (2012); Sanofi-Aventis (2015); Yang et al. (2015).

^dBristol-Myers Squibb (2016); Inoue et al. (2004); Janus et al. (2010); Watanabe et al. (2003).

^eEli Lilly (2014); Ide et al. (2011); Janus et al. (2010); Kiani et al. (2003); Masumori et al. (2008); Siefker-Radtke et al. (2016); Takakura et al. (2014).

^fAshizawa et al. (2010); Czock, Rasche, Boesler, Shipkova, & Keller (2009); Fujita et al. (2011); Kim, Kim, Chung, & Park (2009); Pfizer (2016a); Togashi et al. (2011).

^gBristol-Myers Squibb (2011); Janus et al. (2010); Tanaka (2015).

^hCelgene (2015).

ⁱBrandes, Grossman, & Ahmad (2006); Eli Lilly (2013); Ohana, Brahim, & Ibrahim (2016); Rombola et al. (2015).

^jJanus et al. (2013); Jen et al. (2000); Merck (2008).

^kHerrington, Figueroa, Kirstein, Zamboni, & Stewart (2001); Novartis (2015); O'Reilly et al. (1996).

^lGlaxoSmithKline (2002); Janus et al. (2010); Sahni, Choudhury, & Ahmed (2009).

ing cisplatin as a means of reversing the overdose, which ultimately led to mortality. Despite immediate HD and subsequent plasmapheresis, there were no improvements in toxicity related to the drug concentration of cisplatin (Charlier, Kintz, Dubois, & Plomteux, 2004).

Carboplatin: Carboplatin dosing is unique as it uses the Calvert formula, which calculates a dose that targets a specific area under the curve (AUC). This formula is based on a patient's glomerular filtration rate (GFR). The dose equals the desired AUC multiplied by the sum of 25 and the GFR (Calvert et al., 1989). The GFR represents the extent to which the blood is being actively filtered by the kidneys. Patients on HD no longer have functioning kidneys, and as such, the GFR in the Calvert formula for a patient on HD is set to zero. The target AUC is specific to each regimen and can range from 2 to 7.

Table 2 summarizes several case studies evaluating the use of carboplatin in ESRD patients. Some of these reports include patients receiving HD after the completion of the carboplatin infusion. Approximate AUCs obtained from these patients trended lower than the targeted AUC. This may have been attributed to the HD removing active platinum before goal levels in the plasma were reached (Takezawa, Okamoto, Fukuoka, & Nakagawa, 2008). Another group of case studies showed results closer to target AUCs. These cases timed the HD on the day after the carboplatin infusion potentially removing less active drug. Dosing the day after HD provided a desirable therapeutic outcome and was well tolerated (Kodama et al., 2010, Oguri et al., 2010).

In a comprehensive review paper, the authors concluded carboplatin should be dosed with the Calvert formula using a GFR of 0 and administered 12 to 24 hours before HD (Janus et al., 2010). Carboplatin can be tolerable and appropriate for cancer patients receiving HD the day after treatment as long as proper follow-up is provided.

Taxanes

The taxanes, often used in regimens with the platinum agents, are primarily metabolized via the hepatic system. Taxanes work by inhibiting the polymerization of microtubules, which prevents cells from undergoing mitosis.

Paclitaxel: Generally, ESRD patients can receive full-dose paclitaxel and maintain similar plasma concentrations before and after HD as it is not dialyzable (Baur, Fazeney-Doerner, Olsen, & Dittrich, 2008; Ide et al., 2011; Kodama et al., 2010; Tomita, Kurata, Aoki, Tanaka, & Kazama, 2001; Watanabe et al., 2002; Yoshida, Sumi, Abe, & Ishiko, 2009).

Docetaxel: Docetaxel is also not dialyzable, which allows it to be infused before or after HD and without a dose adjustment. The body eliminates the majority of docetaxel via fecal excretion (Sanofi-Aventis, 2015).

Nab-paclitaxel: Nab-paclitaxel is an albumin-bound form of paclitaxel with only 4% of the drug excreted as unchanged drug and less than 1% as its main metabolites (Celgene, 2015). Considering the metabolic and elimination pathways occur predominately in the liver, dose adjustments are not required for initiating treatment in patients with ESRD, as seen in Table 2.

Topoisomerase I Inhibitors

Irinotecan: Irinotecan binds topoisomerase I and forms a complex with DNA strands, preventing DNA from properly replicating and repairing itself. Nearly 80% of irinotecan's elimination is done without the kidneys (Pfizer, 2016a). The metabolism of irinotecan, however, is complex and dependent on pharmacogenomics. The first step in its metabolism involves the formation of SN-38, a nondialyzable, active metabolite further broken down by UGT1A1 via enzymatic glucuronidation occurring in the liver. Some patients have alleles affecting the expression of this enzyme leading to higher SN-38 levels, and therefore more profound neutropenia (Togashi et al., 2011). Current recommendations from the available literature do not call for proactive UGT1A1 genotyping for patients beginning treatment with irinotecan (Evaluation of Genomic Applications in Practice and Prevention Working Group, 2009).

One case study discussed a small cell lung cancer patient who received irinotecan at a dose of 100 mg/m² weekly for 3 weeks every 28 days (Kim, Kim, Chung, & Park, 2009). Hemodialysis occurred approximately 1 day after each infusion. Treatment was tolerated with grade 2 fatigue and anorexia, and one grade 3 neutropenia event. The

patient achieved a complete response. However, another report documented a small cell lung cancer patient who was scheduled to receive a similar frequency of irinotecan at a lower dose of 50 mg/m², but could not continue treatment after the first dose due to grade 4 neutropenia and a worsening of performance status.

Pharmacogenomics played a role in this high-grade adverse event as the patient had the suspect alleles. Pharmacokinetic (PK) studies performed documented an AUC of the active metabolite SN-38 approximately 3 times greater than that for those with normal renal function, likely because SN-38 is not dialyzable and the genetic predisposition of the patient in question (Togashi et al., 2011).

The caveat for using irinotecan in patients receiving HD is the consideration of possible pharmacogenomic alleles that will change the metabolism of the active metabolite. As long as the patient does not have the alleles that cause a decrease in metabolism of SN-38, it is plausible to consider the use of irinotecan with a reduced dose, and titrate accordingly.

Topotecan: Topotecan binds with DNA and topoisomerase I, stabilizing the cleavable complex preventing religation, thus interrupting DNA replication. There are both IV and oral formulations. The IV drug is excreted by the kidneys with 51% excreted in urine, whereas only 20% of the oral formulation is excreted in urine (Novartis, 2015). The package labeling recommends dose reductions in renal dysfunction, as seen in Table 2.

A case series of 28 patients with documented solid tumors stratified them based on renal function: Group 1 with creatinine clearance (CrCl) ≥ 60 mL/min, Group 2 with CrCl = 40–59 mL/min, Group 3 with CrCl = 20–39 mL/min, and Group 4 with CrCl < 20 mL/min. Dosing of topotecan were 1.5 mg/m²/day for 5 days for Group 1 and 0.5 mg/m²/day for 5 days for the remaining groups with escalation to 1 and 1.5 mg/m². There were two patients with severe renal impairment and one experienced dose-limiting thrombocytopenia during his/her first cycle of 0.5 mg/m²/day. A reduction in clearance was observed in patients with a CrCl < 60 mL/min; however, no relationship between AUC and myelotoxicity was observed. A reduction in the initial dose of topotecan by 50%–75% is rec-

ommended in patients with severe renal dysfunction (O'Reilly et al., 1996).

One case report on an ovarian carcinoma patient with ESRD observed a 60% reduction of topotecan administered on nondialysis days and saw a 4-fold increase in clearance while on HD and systemic clearance similar to that for patients with normal renal function. Despite the increase in clearance, initial observations of plasma concentrations after HD increased. No further investigation was pursued on this rebound effect given logistical concerns. Grade 4 neutropenia and grade 3 thrombocytopenia were observed in the patient without the support of growth factors (Herrington et al., 2001).

Pyrimidine Antagonist

Gemcitabine: Gemcitabine, a prodrug, exerts its antineoplastic effects via its active metabolites acting as a pyrimidine nucleoside analog and inhibiting ribonucleotide reductase, lessening the amount of deoxynucleoside triphosphates available for DNA formation. The parent compound, metabolized by deamination that occurs in the liver, kidneys, and other tissues, becomes 2',2'-difluorodeoxyuridine (dFdU; Kiani et al., 2003). According to prescribing information, over 90% of the drug is excreted in the urine as dFdU and less than 10% as the parent compound (Eli Lilly, 2014). Much of the literature for dose adjustment in HD is derived from the pancreatic cancer patient population.

One case study documented a urothelial carcinoma patient on HD who received treatment with biweekly gemcitabine dosed at 2,250 mg/m² along with paclitaxel. The gemcitabine was reduced by 10% and administered 24 hours before HD. The AUCs were measured for both and were similar to those for a patient with normal renal function. No grade 3 or 4 adverse events were reported, and the patient did not have any documented progression 1 year out from publication (Ide et al., 2011).

A case report on a patient with pancreatic cancer who received 1,000 mg/m² gemcitabine doses on days 1 and 10 for 2 cycles with HD approximately 24 hours after each infusion evaluated levels of gemcitabine and its inactive metabolite, dFdU. Peak serum concentrations and AUC for gemcitabine matched closely to values reported in patients with normal renal function. Interestingly,

dFdU elimination was distinctly decreased for this patient, leading to an AUC approximately 10 times that observed in a patient with normal renal function. Levels of dFdU are known to be eliminated via the urine and the levels in this patient were normalized once HD occurred. The cytotoxic and active metabolites levels more closely mirrored and plateaued like the levels of the parent compound (Kiani et al., 2003).

Another case series is available in which levels of gemcitabine and dFdU were measured for two pancreatic cancer patients on HD receiving gemcitabine at 1,000 mg/m². Similar results were reported where the AUC and peak concentrations of the parent gemcitabine matched those of a population with normal renal function. As previously reported, the dFdU levels were most impacted by the compromised renal function. Until HD was administered, these levels remained notably higher than those for patients with normal renal function (Masumori et al., 2008).

Data regarding increased exposure to this metabolite is limited. Concern exists with gemcitabine's use due to the delayed elimination and higher AUC of dFdU. The current literature indicates that dFdU is a noncytotoxic metabolite and patients with increased exposure do not have an increase in adverse events. Based on this, gemcitabine can be used if needed in the ESRD population without an initial dose reduction as long as careful toxicity monitoring is performed. Gemcitabine can be administered 6 to 12 hours before HD to prevent the possible accumulation of dFdU.

Topoisomerase II Inhibitor

Etoposide: Etoposide acts by binding with DNA and topoisomerase II leading to the destruction of DNA. This drug is excreted by the kidneys with 56% of a dose found in the urine (45% as unchanged drug). Bile and stool account for the remaining 44% that is excreted (Bristol-Myers Squibb, 2016). With respect to the amount of etoposide eliminated by the kidneys, dose reductions for patients on HD are prudent with an effort to keep antitumor activity.

A case series of five ESRD patients who received etoposide at 50 mg/m² on days 1, 3, and 5 is available (Watanabe et al., 2003). Two of the five patients tolerated a dose escalation to the full 100

mg/m² dose of etoposide. All five patients experienced grade 2 or greater anemia and neutropenia starting with the first cycle with full recovery in all cases. Despite a low sample size, this is much higher than the incidence of 33% or less reported in the package labeling for anemia in the general population for etoposide.

Another study evaluated three small cell cancer patients undergoing HD who received etoposide at a 50% dose reduction and had HD 1 hour following the etoposide infusion. These patients received etoposide on days 1 and 3 to ensure it was tolerated appropriately. The authors noted that plasma concentrations obtained were comparable with the levels of patients with normal renal function (Inoue et al., 2004).

Etoposide dose reductions are still pertinent since a small amount of the drug is excreted via the urine and a prolonged half-life can be seen. As it seems, HD does not primarily remove etoposide; therefore, etoposide can be administered before or after HD sessions.

Triazine

Temozolomide: Temozolomide undergoes spontaneous conversion through hydrolysis to the active alkylating agent, methyl-(triazene-1-yl)-imidazole-4-carboxamide, which methylates DNA at the O⁶, N⁷ guanine position leading to double-strand breaks in DNA. Approximately 38% is excreted as parent drug in the urine (Merck, 2008).

There is a paucity of published literature in regards to the dosing of temozolomide in the setting of renal dysfunction. One PK evaluation of 445 patients undergoing trials in the treatment of tumors, including brain metastasis, lung cancer, and breast cancer, concluded that patients with mild to moderate renal dysfunction have similar PK as patients with normal renal function. No evaluation of severe renal dysfunction was reported (Jen et al., 2000).

Vinca Alkaloid

Vinorelbine: Vinorelbine, a semisynthetic vinca alkaloid, prevents the polymerization of tubulin and formation of mitotic spindle. The majority of vinorelbine is excreted in feces (46%), with 18% found in urine. A fraction of vinorelbine is excreted through the kidneys. There are no manufactur-

er recommendations for initial dose adjustment (GlaxoSmithKline, 2002).

In a comprehensive review paper, the authors affirm the recommendations to reduce initial doses to 20 mg/m²/week. Higher doses of 25 mg/m²/week observed neutropenia. There is no current data evaluating oral vinorelbine. The PK data with vinorelbine in HD has not been studied; therefore, recommendations are to administer after HD sessions or on nondialysis days (Janus et al., 2010).

Antimetabolite

Pemetrexed: Pemetrexed, like methotrexate, is an antifolate. It impairs cell division by inhibiting thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase. The inhibition of these enzymes help prevent the de novo creation of purine nucleotides. Approximately 70% to 90% of unchanged pemetrexed is cleared through the urine (Eli Lilly, 2013).

A patient with normal renal function (a CrCl of around 75 mL/minute) was being treated for mesothelioma with pemetrexed at 500 mg/m² and cisplatin (Brandes, Grossman, & Ahmad, 2006). This patient developed acute tubular necrosis following his second cycle and was admitted. In an effort to prevent further toxicity, HD was administered. The levels of pemetrexed in the post dialysate fluid compared to plasma levels pre- and post-HD led the authors to conclude that pemetrexed is poorly dialyzable. Pemetrexed should not be considered for patients without adequate renal function.

A case report of a 70-year-old female with stage IVa non-small cell lung cancer (NSCLC) with CrCl < 45 mL/min received four cycles of carboplatin and pemetrexed then maintenance with pemetrexed at 500 mg/m² every 3 weeks. At dose 14 the dose was reduced to 400 mg/m² and at dose 16 the interval was extended to every 4 weeks. The patient received 51 doses of pemetrexed with estimated GFR (eGFR) ranging from 25–55 mL/min. This is one of the few cases reported of pemetrexed administration in a patient with CrCl < 45 mL/min (Ohana, Brahim, & Ibrahim, 2016). Dialysis remains a contraindication for patients receiving pemetrexed, and giving pemetrexed to a patient with a CrCl < 45 could result in serious chemotherapy toxicities and should be strongly avoided.

TARGETED AGENTS

Monoclonal Antibodies

The therapeutic class of monoclonal antibodies (mAbs) has become an important component of therapeutic regimens in oncology. Antibodies function as individual cytotoxic agents and utilize several mechanisms, including the antigen-binding fragment (Fab) and/or Fc domains of the molecule, serving as a carrier, or by ferrying the toxic cargo to cancer cells. Monoclonal antibodies have several advantages compared to the traditional chemotherapeutic agents, including a prolonged half-life and high target specificity (Glassman & Balthasar, 2014).

Given the size of mAbs, their elimination follows a unique pathway. Target-mediated drug disposition is described as the disposition of mAbs when bound to their molecular target, leading to degradation of the mAb-target complex. Target-mediated drug disposition (TMDD) is mediated either through fluid phase or receptor-mediated endocytosis (Panoilia et al., 2015). Monoclonal antibody-target complexes initiate endocytosis and intracellular elimination of the antibody. As more doses of mAb are administered, target receptor occupancy becomes saturated, leading to a decrease in apparent volume of distribution (Vd). A decrease in Vd results in a decrease in the rate of antibody clearance. This follows a nonlinear, dose-dependent PK model, which does not affect renal clearance (Glassman & Balthasar, 2014).

IV Targeted Therapy

Bevacizumab: Bevacizumab (Avastin), a recombinant humanized mAb, is a vascular endothelial growth factor (VEGF) inhibitor (Genentech, 2016a; Table 3). The main elimination pathway is proteolytic catabolism throughout the body (linear, nonspecific clearance) and not hepatic metabolism or renal excretion (Panoilia et al., 2015). When bevacizumab was administered in a 23-year-old with metastatic renal cell carcinoma undergoing HD, the authors concluded that 5 mg/kg dosing could be used. Based on the plasma levels drawn, they also concluded that bevacizumab is not dialyzable; therefore, the timing of HD in relation to the infusion is not significant (Garnier-Viougat et al., 2007). Bevacizumab can be given without dose reduction due to its larger molecular

Table 3. Intravenous Targeted Therapy for Lung Cancer

Medication	Indication	Dose	Metabolism/elimination	Molecular weight
Bevacizumab	<ul style="list-style-type: none"> Nonsquamous NSCLC with carboplatin and paclitaxel for first-line treatment of unresectable, locally advanced, recurrent or metastatic disease 	15 mg/kg once every 3 weeks	Proteolytic catabolism (linear, nonspecific clearance); half-life is 20 days	149 kDa
Necitumumab	<ul style="list-style-type: none"> EGFR antagonist in combination with gemcitabine and cisplatin for first-line treatment of patients with metastatic squamous NSCLC; not indicated for nonsquamous NSCLC 	800 mg on day 1 and 8 of every 3 weeks	Saturable receptor-mediated clearance; half-life is 7 days	144.8 kDa
Ramucirumab	<ul style="list-style-type: none"> In combination with docetaxel for the treatment of metastatic NSCLC with disease progression on or after platinum-based chemotherapy. Patients with <i>EGFR</i> or <i>ALK</i> genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving ramucirumab 	10 mg/kg once every 3 weeks	Saturable receptor-mediated clearance; half-life is 14 days	147 kDa

Note. NSCLC = non-small cell lung cancer; EGFR = epidermal growth factor receptor; ALK = anaplastic lymphoma kinase.

weight of 149 kDa, which would explain its inability to be dialyzed (Inauen et al., 2007).

Necitumumab: Necitumumab (Portrazza) is a recombinant human immunoglobulin G1 (IgG1) epidermal growth factor receptor (EGFR) mAb that binds to the ligand binding site of the EGFR receptor to prevent receptor activation and downstream signaling (Thatcher et al., 2015). There is no available literature through PubMed or from the manufacturer with regards to dosing and experience in patients undergoing dialysis (Eli Lilly, 2015; Table 4).

Ramucirumab: Ramucirumab (Cyramza) is a recombinant mAb that inhibits vascular endothelial growth factor receptor 2 (VEGFR2) and leads to inhibition of ligand-induced proliferation and migration of endothelial cells (Spratlin,

2010). VEGFR2 inhibition results in reduced tumor vascularity and growth (Fuchs et al., 2014). There is no available literature through PubMed or from the manufacturer with regards to dosing and experience in patients undergoing dialysis (Eli Lilly, 2017).

Oral Targeted Therapy

The oral tyrosine kinase EGFR and ALK (anaplastic lymphomas kinase) inhibitors have truly revolutionized the treatment of patients with NSCLC. Patients harboring these mutations have the ability to be treated with targeted oral agents before cytotoxic chemotherapy or immunotherapy. Of the available eight agents listed in Table 5, there is little to no renal involvement with regards to metabolism or excretion. With that being said,

Table 4. Renal Dose Adjustments for IV Targeted Therapy for Lung Cancer per Package Inserts

Drug	Mild impairment	Moderate impairment ^a	Severe impairment ^b	Dialysis
Bevacizumab	N/A	N/A	N/A	N/A
Necitumumab	N/A	N/A	N/A	N/A
Ramucirumab	N/A	N/A	N/A	N/A

Note. IV = intravenous.
^aCreatinine clearance > 30 mL/min not requiring dialysis.
^bCreatinine clearance 15–29 mL/min.

Table 5. Targeted Therapy for Lung Cancer

Medication	Indication	Dose	Excretion	Metabolism
Afatinib	<ul style="list-style-type: none"> • First-line treatment of patients with metastatic NSCLC with <i>EGFR</i> exon 19 deletions or exon 21 (L858R) substitutions • Patients with metastatic squamous NSCLC who have progressed after platinum-based chemotherapy 	40 mg once daily	Feces (85%); urine (4%)	Minimal enzymatic metabolism
Brigatinib	<ul style="list-style-type: none"> • Patients with <i>ALK</i>+ metastatic NSCLC who have progressed or are intolerant to crizotinib 	90 mg once daily	Feces (65%); urine (25%)	Hepatic (CYP2C8, CYP3A4)
Erlotinib	<ul style="list-style-type: none"> • Patients with <i>EGFR</i>+ metastatic NSCLC with exon 19 deletions or exon 21 (L858R) substitutions receiving first-line, maintenance, or second- or greater-line therapy after progression following at least one prior regimen 	150 mg once daily	Feces (83%); urine (8%)	Hepatic
Gefitinib	<ul style="list-style-type: none"> • Patients with first-line metastatic NSCLC who have <i>EGFR</i> exon 19 deletions or exon 21 (L858R) substitutions 	250 mg once daily	Feces (86%); urine (< 4%)	Hepatic
Osimertinib	<ul style="list-style-type: none"> • Patients with metastatic NSCLC who have <i>EGFR</i> T790M mutations and have progressed on or after <i>EGFR</i> TKI therapy 	80 mg once daily	Feces (68%); urine (14%)	Hepatic
Crizotinib	<ul style="list-style-type: none"> • Patients with metastatic <i>ALK</i>+ or <i>ROS1</i>+ NSCLC 	250 mg twice daily	Feces (63%); urine (22%)	Hepatic (CYP3A4/5)
Ceritinib	<ul style="list-style-type: none"> • Patients with <i>ALK</i>+ metastatic NSCLC who have progressed or are intolerant to crizotinib 	750 mg once daily	Feces (92%); urine (1%)	Hepatic
Alectinib	<ul style="list-style-type: none"> • Patients with <i>ALK</i>+ metastatic NSCLC who have progressed or are intolerant to crizotinib 	600 mg twice daily	Feces (98%); urine (< 0.5%)	Hepatic

Note. NSCLC = non-small cell lung cancer; *EGFR* = epidermal growth factor receptor; *ALK* = anaplastic lymphoma kinase; CYP = cytochrome P450; TKI = tyrosine kinase inhibitor; *ROS1* = ROS proto-oncogene 1.

there is limited PK and pharmacodynamic burden on the kidneys; however, there is also a paucity of manufacturer-recommended renal dose adjustments, as noted in Table 6.

Erlotinib: More literature and experience exists in dosing the *EGFR* inhibitors in dialysis patients than there is in dosing patients with the *ALK* inhibitors. A PK analysis of the active metabolite of erlotinib (Tarceva) was performed and compared in three patients with NSCLC and chronic renal failure (CRF) undergoing noncancer-related dialysis and five patients with NSCLC with normal organ function. The three intervention patients were all offered unadjusted erlotinib instead of chemotherapy due to the greater perceived benefit, even though their *EGFR* mutation

status was negative or unknown. Two of the three patients experienced diarrhea as an adverse event, with one of those patients also having nausea and the remaining patient having no major toxicities while on treatment. Pharmacokinetic analyses among the case and control patients were similar, indicating that erlotinib was not affected by dialysis. All three dialysis patients had a response to therapy, with two having stable disease and one patient having a partial response (Togashi et al., 2010). The manufacturer also shared information about patients on chronic dialysis who tolerated full-dose erlotinib and achieved stable disease for 11 months as first-line treatment of NSCLC. No further outcomes were described (Genentech/As-tellas Oncology, 2016).

Table 6. Renal Dose Adjustments for Targeted Lung Cancer Therapy per Package Inserts

Drug	Mild impairment	Moderate impairment ^a	Severe impairment ^b	Dialysis
Afatinib	N/A	N/A	30 mg once daily	N/A
Brigatinib	N/A	N/A	N/A	N/A
Erlotinib	N/A	N/A	N/A	N/A
Gefitinib	N/A	N/A	N/A	N/A
Osimertinib	N/A	N/A	N/A	N/A
Crizotinib	N/A	N/A	250 mg once daily	N/A
Ceritinib	N/A	N/A	N/A	N/A
Alectinib	N/A	N/A	N/A	N/A

Note. ^aCreatinine clearance > 30 mL/min not requiring dialysis.

^bCreatinine clearance 15–29 mL/min.

Gefitinib: In a similar manner to erlotinib, there are case reports and information from the manufacturer on gefitinib (Iressa) in patients who are receiving HD. The earliest reported case from 2007 was that of a 58-year-old, never-smoking female on HD. Molecular testing revealed an *EGFR* exon 19 deletion mutation. The patient started full-dose therapy with gefitinib and continued her dialysis. Blood samples taken around dialysis revealed that the PK pattern was similar to that of a patient with normal renal function, stating that 88.7% of the gefitinib was kept in the plasma through dialysis. She achieved a response to therapy throughout the 13-month course and had no significant adverse events (Shinagawa et al., 2007).

Two other case reports are also described in elderly never-smoking male patients. In the first case, a 70-year-old patient on HD was treated with full-dose gefitinib for his recurrent *EGFR* exon 19 deletion–positive NSCLC. He demonstrated a complete response to treatment with no significant adverse events (Del Conte et al., 2014). In the second case, a 72-year-old patient on continuous ambulatory peritoneal dialysis (CAPD) was also treated with full-dose gefitinib for recurrent *EGFR* exon 19 deletion–positive NSCLC metastatic to the brain. Blood samples obtained during the patient's treatment around CAPD were deemed to reach steady state by day 16, and drug concentrations were minimally impacted by CAPD. The patient developed grade 2 diarrhea as his only side effect and had disease improvement. (Yamaguchi, Isogai, & Okamura, 2015). However, there are considerable differences in the contents of the dialy-

sate and the timing and volume of dialysis fluid exchange among individual CAPD patients, which make these results difficult to generalize.

Afatinib: Unlike the previously mentioned therapies, afatinib (Gilotrif) had no information from the manufacturer with regards to PK studies or experience in patients receiving HD. However, there have been case reports from which interpretations of safety and efficacy can be drawn. The first case report published was on a 60-year-old female never smoker with unknown *EGFR* status and CRF. The patient observed clinical benefit and prolonged response of disease for 7 years. Upon progression, the patient was placed on afatinib at 30 mg daily. The patient tolerated therapy well through continued dialysis for 2 months, experiencing only mild asthenia. Therapy was then increased to full dose at 40 mg daily (Boehringer Ingelheim, 2016).

Unfortunately, after only a few days, due to the appearance of significant asthenia and vomiting and nausea, the patient self-discontinued therapy and was off therapy until she had progression of disease in March 2012 (Bersanelli, Tiseo, Artioli, Lucchi, & Ardizzoni, 2014). This is the only available example of a patient who experienced side effects severe enough to discontinue therapy among the case examples for targeted therapy during dialysis.

Another more recent case report recounted three male patients on dialysis three times weekly with good performance status, ages 62 to 78, two with exon 19 deletion–positive disease and one with exon 21 mutation–positive disease. All patients were given reduced-dose afatinib at 30 mg daily and observed partial responses in their dis-

ease without significant side effects. Most notably, PK analyses based on blood samples taken on days before and after dialysis were similar to those in patients with normal organ function (Boehringer Ingelheim, 2016; Imai et al., 2016).

Osimertinib: The third-generation EGFR inhibitor and only treatment for T790M mutation-positive disease, osimertinib (Tagrisso), has no available literature available through PubMed or from the manufacturer with regards to dosing and experience in patients undergoing dialysis (AstraZeneca, 2015).

Alectinib: Of the available ALK inhibitors, alectinib (Alecensa) was the only agent to have any literature on use in a patient on dialysis. In the dose-finding portion of the phase 1/2 AF-002JG study, a patient taking dose-reduced alectinib at 460 mg twice daily developed grade 4 acute renal failure secondary to a family history of hyperoxaluria associated with kidney stones. Therapy was withheld during workup and the patient started dialysis. After 60 days off treatment, the patient resumed alectinib at the same reduced dose. The patient remained on alectinib for more than 1.5 years, despite continued dependence on HD (Gadgeel et al., 2014; Genentech, 2015).

Crizotinib, Brigatinib, and Ceritinib: The other available ALK inhibitor therapies, crizotinib (Xalkori), brigatinib (Alunbrig), and ceritinib (Zykadia), have no available literature available through PubMed or from the manufacturer with regards to dosing and experience in patients undergoing dialysis (Novartis, 2016; Pfizer, 2016b; Takeda, 2017).

Immunotherapy

Immunotherapy has revolutionized the cancer treatment paradigm by harnessing the patient's own immune system to target evading cancer cells (Table 7). The first US Food and Drug Administration approvals for non-small cell lung cancer within this category were nivolumab (Opdivo) and pembrolizumab (Keytruda), based on response rates and durable overall survival data.

Nivolumab: Nivolumab is a fully human immunoglobulin G4 (IgG4) mAb that selectively inhibits programmed cell death protein 1 (PD-1) activity by binding to the PD-1 receptor to block the ligands PD-L1 and PD-L2 (Bristol-Myers Squibb, 2017).

The negative PD-1 receptor signaling that regulates T-cell activation and proliferation is disrupted, resulting in the inhibition of the immune response, including the antitumor immune response (Robert, 2015). There is no information from the manufacturer with regards to PK studies or experience in patients on dialysis (Table 8). However, there have been case reports that have shown nivolumab can be safely administered to ESRD patients. A 77-year-old male with metastatic clear cell renal cell carcinoma received fourth-line nivolumab while on dialysis; however, the timing of the dialysis in relation to the administration of nivolumab was not mentioned in the case report. The patient received 8 doses of nivolumab and showed significant disease improvement (Carlo & Feldman, 2016).

Pembrolizumab: Pembrolizumab is a selective humanized IgG4- κ mAb that inhibits the PD-1 receptor, which plays a pivotal role in immune checkpoint regulation in the tumor microenvironment (Dang, Ogunniyi, Barbee, & Drilon, 2016). Blocking the PD-1 pathway inhibits the negative immune regulation caused by PD-1 receptor signaling (Hamid, 2013). There is no information from the manufacturer with regards to PK studies or experience in patients on dialysis (Merck, 2016). However, there have been case reports that have shown pembrolizumab can be safely administered to ESRD patients. A 63-year-old male with metastatic melanoma was treated with pembrolizumab while on dialysis. The patient received dialysis three times a week and completed 10 cycles of pembrolizumab, and last reported with a complete remission. Due to the size of the antibodies, the authors suggested that pembrolizumab can be given without regard to the timing of dialysis (Chang & Shirai, 2016).

Atezolizumab: Atezolizumab (Tecentriq) is a humanized mAb immune checkpoint inhibitor that binds to PD-L1 to selectively prevent the interaction between PD-1 and B7-1 (CD80) receptors (Fehrenbacher et al., 2016). There is no available literature through PubMed or from the manufacturer with regards to dosing and experience in patients undergoing dialysis (Genentech, 2016b).

CONCLUSION

In summary, many drugs used in the treatment of lung cancer may be safely administered to patients

Table 7. Immunotherapy for Lung Cancer

Medication	Indication	Dose	Metabolism/elimination	Molecular weight
Atezolizumab	<ul style="list-style-type: none"> Patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy Patients with <i>EGFR</i> or <i>ALK</i> genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving atezolizumab 	1,200 mg once every 3 weeks	T-cell mediated elimination; half-life is 27 days	145 kDa
Nivolumab	<ul style="list-style-type: none"> Treatment for metastatic NSCLC and progression on or after platinum-based chemotherapy Patients with <i>EGFR</i> or <i>ALK</i> genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving nivolumab 	240 mg once every 2 weeks	N/A; half-life is 27 days	146 kDa
Pembrolizumab	<ul style="list-style-type: none"> Treatment for metastatic NSCLC with high PD-L1 expression (TPS \geq 50%) with no <i>EGFR</i> or <i>ALK</i> genomic tumor aberrations, and no prior systemic chemotherapy treatment Treatment for metastatic NSCLC with PD-L1 expression (TPS \geq 1%) with disease progression on or after platinum-containing chemotherapy Patients with <i>EGFR</i> or <i>ALK</i> genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab 	200 mg once every 3 weeks	Phagocytosis by cells of the reticuloendothelial system into fragment and then renally eliminated; half-life is 26 days	149 kDa

Note. NSCLC = non-small cell lung cancer; EGFR = epidermal growth factor receptor; ALK = anaplastic lymphoma kinase; PD-L1 = programmed cell death ligand 1; TPS = tumor proportion score.

who are undergoing HD. Although these patients may have several comorbid conditions and multiple medications to manage, they can still be offered treatment for lung cancer. Dose adjustments and the timing of HD in regards to the administration of chemotherapy, immunotherapy, and targeted agents must be taken into consideration. There is

a paucity of data and case studies with targeted agents and immunotherapy. It is imperative for clinicians to document and add to the body of evidence on the use of these agents in patients receiving HD. Clinicians must follow package inserts and clinical experiences in the management of these patients to mitigate serious complications. ●

Table 8. Renal Dose Adjustments for Immunotherapy for Lung Cancer per Package Inserts

Medication	Mild impairment	Moderate impairment ^a	Severe impairment ^b	Dialysis
Atezolizumab	N/A	N/A	N/A	N/A
Nivolumab	N/A	N/A	N/A	N/A
Pembrolizumab	N/A	N/A	N/A	N/A

Note. ^aCreatinine clearance > 30 mL/min not requiring dialysis.

^bCreatinine clearance 15–29 mL/min.

Disclosure

Ms. Eaby-Sandy has served in a consultant role for AbbVie and Ariad/Takeda, and has served on speakers bureaus for Amgen, AstraZeneca, Helsinn, and Merck. Dr. Leung, Dr. Hughes, Dr. Cambareri, and Dr. Rubin have no conflicts of interest to disclose.

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