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REVIEW ARTICLE

Decreased Disposition of Anticancer Drugs Predominantly Eliminated *via* the Liver in Patients with Renal Failure

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Abstract: ***Background*:** Evidence has revealed that renal impairment can affect the systemic exposure of drugs which are predominantly eliminated *via* the liver. The modulation of drug-metabolizing enzymes and transporters expressed in the liver and/or small intestine by diverse entities, including uremic toxins, in systemic circulation of patients with severe renal failure is considered as the cause of atypical pharmacokinetics, which sometimes induce undesirable adverse events that are especially critical for drugs with narrow therapeutic window such as anticancer drugs. A dosing strategy for anticancer drugs in these patients needs to be established.

***Methods*:** The effects of renal impairment on the systemic exposure and safety of anticancer drugs were summarized. The proposed mechanisms for the alterations in the pharmacokinetics of these anticancer drugs were also discussed.

***Results*:** Changes in pharmacokinetics and clinical response were reported in 9 out of 10 cytotoxic anticancer drugs investigated, although available information was limited and sometimes controversial. Systemic exposure of 3 out of 16 tyrosine kinase inhibitors was higher in patients with severe renal failure than that in patients with normal kidney function. An increase in systemic exposure of anticancer drugs in patients with renal impairment is likely to be observed for substrates of OATP1B1, despite the limited evidence.

***Conclusion*:** The molecular basis for the effect of uremia on non-renal drug elimination still needed to be clarified with further studies to generate generalizable concepts, which may provide insights into establishing better clinical usage of anticancer drugs, *i.e.* identifying patients at risk and dose adjustment.

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1. INTRODUCTION

Many recent studies have revealed that drug-metabolizing enzymes and uptake/efflux transporters in the liver are differentially influenced by severe renal failure [1, 2]. Therefore, even drugs that are predominantly disposed to hepatic metabolism and/or transport can be modified by severe renal failure to reduce their non-renal clearance; this may sometimes result in unexpected consequences such as atypical pharmacokinetics and an elevated risk of adverse events. High levels of uremic toxins in the plasma of severe renal failure patients proved to be, at least in part, implicated in these effects. Atypical drug responses are clinically important especially for drugs with narrow therapeutic windows such as anticancer drugs.

Since the initial use of nitrogen mustards to treat malignant lymphoma, numerous cytotoxic chemotherapeutic agents have been developed and clinically used to manage a variety of tumors [3]. One of the essential properties of cytotoxic anticancer drugs is that they do not exhibit specific effects on tumor cells; instead, they frequently exhibit dose-dependent cytotoxicity against a range of proliferating cells including the following normal cellular elements: bone marrow, gastrointestinal mucosa, and hair follicles [4]. Dose and treatment-schedule recommendations for cytotoxic anticancer agents are determined based on the dose-limiting toxicity and the maximum-tolerated dose obtained in phase 1 studies, which also characterize the agent's pharmacokinetic properties [5]. Based on these results, the therapeutic window of these agents is generally narrow, and excessive toxicities including myelosuppression and/or diarrhea are commonly observed in practical treatments with cytotoxic anticancer drugs; death from chemotherapy-related toxicity is rare. A slight increase in plasma level of a cytotoxic anticancer drug with a narrow therapeutic window may cause severe drug-related adverse events.

The focus of drug development in oncology has shifted markedly over the past decades from non-tumor-specific cytotoxic anticancer drugs to molecular-targeted agents. To date, various therapeutic drugs that efficiently target and inhibit receptor tyrosine

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kinases, termed receptor Tyrosine Kinase Inhibitors (TKIs), have been developed. TKIs have revolutionized the survival of patients with specific cancers, which raises the hope of many cancer patients who are unresponsive to classical cytotoxic anticancer drugs and/or cytokines [6]. Although receptor TKIs are generally well-tolerated, unexpected toxicities sometimes occur in various organs. For example, TKIs that inhibit the Epidermal Growth Factor Receptor (EGFR) are likely to induce diarrhea or skin rash, while TKIs that target angiogenesis by inhibiting Vascular Endothelial Growth Factor Receptors (VEGFRs) frequently cause hypertension, protein urea, hemorrhage, and/or thrombosis. This indicates that the efficacy and toxic effects of TKIs are often closely linked to each other. These on-target toxic effects can serve as potential biomarkers of effective pharmacological inhibition of the targeted pathway and are reflective of clinically-relevant antitumor effects [7]. Off-target toxicity occurs when a TKI leads to toxicity *via* inhibiting a kinase or other molecules that are not intended as a target of the drug. As such, TKI-related adverse events are frequently associated with systemic exposure to the TKI [8], appropriate control of the plasma concentrations with TKI is suggested to be important.

According to the aforementioned properties of anticancer drugs, it may be plausible that severe renal failure can significantly impact the pharmacokinetics and/or clinical outcomes, although these patients are generally administered an anticancer drug that is predominantly excreted *via* the liver in feces, because of the modulation in the drug-metabolizing enzymes and transporters expressed in the liver and/or small intestine.

In this review, we first summarize the drug-metabolizing enzymes and transporters involved in the non-renal clearance of anticancer drugs predominantly eliminated *via* the liver. We then present the effect of renal impairment on systemic exposure and the safety of these agents. Finally, we will discuss the proposed mechanisms for the alterations of non-renal clearance of these anticancer drugs in patients with renal failure; this is in efforts to discover general concepts which are essential for better clinical usage of anticancer drugs, *i.e.* identifying patients at risk and adjusting their dose.

2. PHARMACOKINETIC PROPERTIES OF ANTICANCER DRUGS MAINLY ELIMINATED *VIA* THE LIVER

To date, many cytotoxic anticancer drugs and TKIs predominantly eliminated *via* the liver in feces have been approved by the US Food and Drug Administration (FDA) and used in clinical practice. The elimination pathways, protein binding, drug-metabolizing enzymes and transporters potentially involved in the pharmacokinetics of cytotoxic anticancer drugs and TKIs are summarized in Table **1** [9-37] and Table **2** [38-67], respectively.

Table 1. Pharmacokinetic properties of cytotoxic anticancer drugs approved by the FDA and mainly eliminated *via* the liver. [a]

Cytotoxic Anticancer Drugs	Target(s)	Elimination Pathways		Protein Binding (%)	Drug-Metabolizing Enzymes	Transporters	References [b]
		Feces (%)	Urine (%)				
Cyclophosphamide	Cross-linking of tumor cell DNA	Primarily metabolized in the liver	10-20	20	CYP2B6 (major), 2A6, 3A4, 3A5, 2C9, 2C18, and 2C19	ABCB1	[9-12]
Docetaxel	Tubulin	75	6	94-97	CYP3A4, 3A5	ABCB1, ABCC2, OATP1B1, OATP1B3	[13-15]
Doxorubicin	Topoisomerase II	40	5-12	74-76	Aldo- keto reductase, carbonyl reductase	ABCB1, ABCG2	[16-19]
Epirubicin	Topoisomerase II	34	27	77	Aldo- keto reductase, carbonyl reductase	ABCB1, ABCG2	[19, 20]
Eribulin	Tubulin	82	9	49-65	CYP3A4	ABCB1	[21]
Etoposide	Topoisomerase II	44	56	97	CYP3A4	ABCB1, ABCG2, ABCC2, ABCC3	[22-25]
5-Fluorouracil	Thymidylate synthase, tumor DNA and RNA	Extensively metabolized in the liver	5-20 (parent drug)	~10 (PMDA, Japan)	Dihydropyrimidine dehydrogenase	No information	
Irinotecan (SN-38)	Topoisomerase I (SN-38)	62	30.2, <1 (SN-38)	30-68, 95 (SN-38)	CES1, CES2, CYP3A4, UGT1A1 (SN-38)	ABCB1, ABCC2, ABCG2, OATP1B1, OATP1B3	[26-28]
Paclitaxel	Tubulin	71	14	89-98	CYP2C8, 3A4	ABCB1, ABCC2, OATP1B1, OATP1B3	[29-33]
Vinorelbine	Tubulin	46	18	79.6-91.2	CYP3A4	ABCB1, ABCC2	[34-37]

a, Information from FDA label is included for each anticancer drug.

b, Number of references is the same as those cited in the text.

ABCB1, ATP-binding cassette sub-family B member 1; ABCC2, ATP-binding cassette sub-family C member 2; ABCC3, ATP-binding cassette sub-family C member 3; ABCG2, ATP-binding cassette sub-family G member 2; CES1, Carboxylesterase 1; CES2, Carboxylesterase 2; CYP, Cytochrome P450; OATP1B1, Organic-anion transporting polypeptide 1B1; OATP1B3, Organic-anion transporting polypeptide 1B3; PMDA, Pharmaceuticals and Medical Devices Agency; SN-38, 7-Ethyl-10-hydroxycamptothecin; UGT1A1, UDP-glucuronosyltransferase 1A1.

Table 2. Pharmacokinetic properties of receptor TKIs approved by the FDA which mainly eliminated *via* the liver. [a]

Receptor TKIs		Target(s)	Elimination Pathways		Protein binding (%)	Drug-Metabolizing Enzymes		Transporters	References[b]
			Feces (%)	Urine (%)		Major	Minor		
EGFR-targeting TKIs									
	Afatinib	EGFR1-4	85	4	95	Michael addition		ABCB1, ABCG2	[38, 39]
	Erlotinib	EGFR	83	8	93	CYP3A4, 3A5, 1A1	CYP1A2	ABCB1	[40, 41]
	Gefitinib	EGFR	86	4	90	CYP3A4, 3A5, 1A1, 2D6		ABCB1, OATP1B3	[41, 42]
	Lapatinib	EGFR1-2	91.8	1.2	>99	CYP3A4, 3A5	CYP2C8, 2C19	ABCB1, ABCG2	[43, 44]
	Osimertinib	EGFR	67.8	14.2	95	CYP3A4, 3A5	CYP1A1	ABCB1, ABCG2	[45, 46]
VEGFR-targeting TKIs (Multi receptor-targeting TKIs)									
	Axitinib	VEGFR1-3	41	23	>99	CYP3A4, 3A5	CYP2C19, 1A2, UGT1A1	ABCB1, ABCG2, OATP1B1, 1B3	[47-49]
	Cabozantinib	RET, MET, VEGFR1-3, KIT, NTRK2, FLT3, AXL, TEK	54	27	>99.7	CYP3A4		ABCC2	
	Lenvatinib	VEGFR1-3, FGFR1-4, PDGFRα, KIT, RET	64	25	98-99	Aldehyde oxidase, CYP3A4, non-enzymatic process		ABCB1, ABCG2	[50]
	Pazopanib	VEGFR1-3, PDGFRα-β, FGFR1,3, KIT, LTK, LCK, CSF-1R	82.2	2.6	>99	CYP3A4	CYP1A2, CYP2C8	ABCB1, ABCG2, OATP1B1, 1B3, OCT1	[42, 51-53]
	Regorafenib	VEGFR1-3, KIT, PDGFRα-β, RET, FGFR1-2, TEK, DDR2, NTRK1, EPHA2, RAF-1, BRAF, BRAFV600E, FRK, Abl	71	19	99.5	CYP3A4, UGT1A9		ABCC2, ABCB1, ABCG2, OATP1B1	[54, 55]
	Sorafenib	VEGFR1-3, PDGFR-ß, KIT, FLT3, RET, RET/PTC	77	19	99.5	CYP3A4, UGT1A9		ABCB1, ABCG2, ABCC2, OATP1B1, OATP1B3	[42, 56-59]
	Sunitinib	VEGFR1-3, PDGFRα-β, KIT, FLT3, CSF-1R, RET	61	16	95	CYP3A4	CYP1A2	ABCB1, ABCG2, OATP1B1	[42, 58-60]
	Vandetanib	EGFR, VEGFR, RET, TEK, EPH, Src	44	25	94	CYP3A4	FMO1, FMO3	OATP1B1, 1B3	[42, 61, 62]
ALK-targeting TKIs									
	Alectinib	ALK, RET	98	<0.5	>99	CYP3A4		No information	[63]
	Ceritinib	ALK, IGF-1R, InsR, ROS1	92.3	1.3	97	CYP3A4		ABCB1, ABCG2	[64, 65]
	Crizotinib	ALK, MET, ROS1, RON	63	22	91	CYP3A4, 3A5		ABCB1, OATP1B1, 1B3	[42, 66, 67]

a, Information from FDA label is included for each anticancer drug.

b, Number of references is the same as those cited in the text.

ABCB1, ATP-binding cassette sub-family B member 1; ABCC2, ATP-binding cassette sub-family C member 2; ABCG2, ATP-binding cassette sub-family G member 2; Abl, Abl proto-oncogene; ALK, Anaplastic lymphoma kinase; AXL, AXL receptor tyrosine kinase; BRAF, B-RAF proto-oncogene; CSF-1R, Colony stimulating factor-1 receptor; CYP, Cytochrome P450; DDR2, Discoidin domain receptor tyrosine kinase 2; EGFR, Epidermal growth factor receptor; EPH, EPH receptor; FGFR, Fibroblast growth factor receptor; FLT-3, Fms-related tyrosine kinase-3; FMO1, Flavin-containing monooxygenase 1; FMO3, Flavin-containing monooxygenase 3; FRK, Fyn-related src family tyrosine kinase; IGF-1R, Insulin-like growth factor-1 receptor; InsR, Insulin receptor; KIT, KIT proto-oncogene receptor tyrosine kinase; LCK, LCK proto-oncogene; LTK, Leukocyte receptor tyrosine kinase; MET, MET proto-oncogene; NTRK, Neurotrophic receptor tyrosine kinase 2; OATP1B1, Organic-anion transporting polypeptide 1B1; OATP1B3, Organic-anion transporting polypeptide 1B3; OCT1, Organic cation transporter 1; PDGFR, Platelet-derived growth factor receptor; PTC, Papillary thyroid carcinoma; Raf-1, Raf-1 proto-oncogene; RET, Rearranged during transfection; ROS-1, ROS proto-oncogene 1; RON, RON tyrosine kinase; Src, Src proto-oncogene; TEK, TEK receptor tyrosine kinase; TKIs, Tyrosine kinase inhibitors; UGT1A1, UDP-glucuronosyltransferase 1A1; UGT1A9, UDP-glucuronosyltransferase 1A9; VEGFR, Vascular endothelial growth factor receptor.

A wide range of protein binding ability exists for cytotoxic anticancer drugs (Table **1**), whereas that of TKIs are >90% (Table **2**). Several TKIs such as sorafenib and regorafenib show extremely high protein binding >99%. Cytochrome P450 (CYP) 3A expressed in the liver is responsible for the inactivation of cytotoxic docetaxel, eribulin, etoposide, irinotecan, paclitaxel, and vinorelbine. Irinotecan is metabolized by carboxylesterase to form the active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38). SN-38 is detoxified by UDP-glucuronosyltransferase (UGT) 1A1 to produce inactive SN-38 glucuronide (SN-38G). Dihydropyrimidine dehydrogenase expressed in the liver is a drug-metabolizing enzyme and catalyzes the rate-limiting step of 5-fluorouracil (5-FU) catabolism. Although a variety of CYP isoforms are involved in the 4-hydroxylation of cyclophosphamide, an initial activation step, CYP2B6 is known to be highly contributed to the process [9-11, 24]. Aldo-keto reductase and carbonyl reductase are the enzymes responsible for the metabolism of anthracyclines, doxorubicin and epirubicin [17-19, 24].

Hepatic CYP3A is responsible for the metabolism of most TKIs, excluding afatinib (Table **2**). This pan-EGFR inhibitor is predominantly subjected to non-enzymatic Michael addition. UGT1A9 is involved in the detoxification of both sorafenib and regorafenib, and the glucuronidation products of these TKIs are mainly excreted in urine. The amount is approximately <20% of the orally administered dose. Most TKIs are substrates for the ATP-binding cassette sub-family B member 1 (ABCB1) and ATP-binding cassette sub-family G member 2 (ABCG2) expressed in the canalicular membrane of hepatocytes and apical membrane of enterocytes. These ABC transporters are considered to play roles in bile excretion and efflux from enterocytes to the intestinal lumen. Some TKIs including axitinib, regorafenib, sorafenib, vandetanib, and crizotinib are reported as substrates of the Organic-anion Transporting Polypeptide (OATP) 1B1 and/or 1B3, which are in the sinusoidal membrane of hepatocytes. These TKIs may be transported into hepatocytes by these solute carriers. Our recent *in vitro* and *in vivo* experiments have revealed that pazopanib is a substrate of the human organic cation transporter 1 [53].

Altering the activity and expression of these drug-metabolizing enzymes and/or transporters may result in an increase or a decrease in hepatic (non-renal) clearance of these anticancer drugs.

3. PHARMACOKINETICS AND CLINICAL RESPONSE OF CYTOTOXIC ANTICANCER DRUGS ELIMINATED NON-RENALLY IN PATIENTS WITH RENAL FAILURE

The effects of renal impairment on the pharmacokinetics and clinical response of the cytotoxic anticancer drugs predominantly eliminated *via* the liver are summarized in Table **3**.

Table 3. Changes in the pharmacokinetics and clinical response of cytotoxic anticancer drugs predominantly eliminated in feces in patients with severe renal failure.

Cytotoxic Anticancer Drugs	Renal Impairment					Note	References
	Mild	Moderate	Severe	Dialysis	Unknown		
Cyclophosphamide		AUC, 38% or 42% ↑ (CLcr, 25 to 50 mL/min)	AUC, 77% ↑ (CLcr, 10-24 mL/min)	AUC, 23% ↑ (CLcr, < 10 mL/min)		Dialyzable	[68, 69]
				AUC, 50% ↑			[70]
		AUC, 67% ↑ (CLcr, 38 mL/min); AUC of active metabolite, 11% ↑ (CLcr, 38 mL/min)					[71]
Docetaxel				AUC and CL, no change; safe (peritoneal dialysis)		Scr, 9.2 mg/dL	[72]
				AUC, no change			[70]
				Tolerable		Scr, 2.6 mg/dL	[73]
Doxorubicin				Doxorubicin CL, ↓ ; AUC, 1.5 times ↑ (AUC doxorubicinol, 3 times ↑)			[74, 75]
				Mean residual time, 2 times ↑			[74]
		Tolerable (CLcr, 30-60 mL/min/1.73 m^2)					[76]
	Toxicity, ↑ ; Dose reduction necessary (CLcr, 16.6-80.4 mL/min/1.73 m^2)					Liposomal doxorubicin	[77]
Epirubicin				Safe			[78]
						CL, 50% ↓ (Scr, > 5 mg/dL)	[75]
Eribulin	AUC, no change (CLcr, 50-79 mL/min)	AUC, 1.5 times ↑ (CLcr, 30-49 mL/min)	AUC, 1.5 times ↑ (CLcr, 15-29 mL/min)			Dose reduction necessary (CLcr, < 50 mL/min)	[79, 80]

Table (3) contd….

Cytotoxic Anti-cancer Drugs	Renal Impairment					Note	References
	Mild	Moderate	Severe	Dialysis	Unknown		
Etoposide	CL, ↓ (Scr, > 1.5 mg/dL and CLcr, < 60 mL/min)					Correlation between drug CL and Scr	[81]
					AUC, ↓; Steady state distribution, ↓		[82]
				AUC, no change			[83-86]
5-Fluorouracil					CL in CKD patient, ↓		[87]
						AUC and CL, no change (Scr, 1.5-3 mg/dL); No relationship between 5-FU CL and Scr	[88]
				AUC, no change			[89]
Irinotecan (SN-38)				AUC, 1.7 fold ↑; AUC (unbound) 4.38 times, ↑ (median CLcr, 7.09 mL/min [range 6.67-13.3])			[91, 92]
				SN-38 CL, ↓			[94]
		SN-38 CL, no change (CLcr, 35-66 mL/min); Grade 3/4 neutropenia, 4 times ↑					[95]
						Safe (Scr, 1.6–5.0 mg/dL)	[96]
Paclitaxel			AUC, 1.5 times ↑ (Scr, < 20 mL/min)				[97]
				PK, no change, Safe			[98-100, 102, 103]
						Not dialyzable	[100]
Vinorelbine				Dose reduction necessary.			[104]

AUC, Area under the plasma concentration-time curve; CKD, Chronic kidney disease; CL, Clearance; CLcr, Creatinine clearance; eGFR, Estimated glomerular filtration rate; GFR, Glomerular filtration rate; PK, Pharmacokinetics; Scr, Serum creatinine.

3.1. Cyclophosphamide

Clearance of cyclophosphamide is decreased in patients with reduced renal function, thereby resulting in an increased systemic drug exposure [68, 69]. The mean area under the plasma concentration-time curve (AUC) corrected by dose increased by 38 or 42% and 77% in the moderate and severe renal impairment groups ($P < 0.05$), respectively when compared to the control group. This suggests that patients with severe renal impairment should be closely monitored for toxicity. The AUC in the hemodialysis group only increased by 23%, suggesting the removal of cyclophosphamide into the dialysate. A patient who underwent hemodialysis treated with cyclophosphamide 600 mg/m^2 and docetaxel 75 mg/m^2 (TC regimen) displayed a 50% increase in drug exposure [70]. In another report, the elimination of cyclophosphamide in a patient with moderate renal insufficiency was also reduced when compared to a reference population, resulting in a 67% increased exposure to this compound [71]. However, exposure to 4-hydroxycyclophosphamide, an active metabolite, only increased by 11%, suggesting that altering the dose of cyclophosphamide in patients with moderate renal impairment is not required.

3.2. Docetaxel

The AUC and clearance of docetaxel in patients who underwent peritoneal dialysis were 2.11 μg/mL·h and 25.1 L/h/m^2 respectively, which are consistent with values previously determined for patients with normal renal function [72]. The occurrence and severity of adverse events associated with docetaxel were also not increased owing to the reduced renal function. Docetaxel AUC was unaffected in a patient who underwent hemodialysis and received regular TC regimen [70]. Furthermore, in a preliminary study including 11 patients with advanced urothelial carcinoma and renal impairment [73], the treatment with 100 mg/m^2 docetaxel was relatively well-tolerated with no treatment-related deaths; an evident relationship between renal function and toxicity did not exist. Overall, the pharmacokinetics and safety of docetaxel were not affected by renal function in serum creatinine (Scr) level up to 9 mg/dL.

3.3. Doxorubicin

The comparative pharmacokinetics of doxorubicin was investigated in 5 hemodialysis and 8 normal patients who were infused with a 40- to 60-mg dose of doxorubicin [74]. Approximately 1.5 and 3 times higher AUC values of both doxorubicin and doxorubicinol were observed in the hemodialysis patients when compared to normal patients, suggesting the need for careful attention to hemodialysis patients receiving doxorubicin. Li *et al*. [75] also reported that clearance of doxorubicin in patients on hemodialysis was lower than that in patients with a normal kidney. On the other hand, doxorubicin was reported to be tolerable in patients with renal impairment [76]. Li *et al*. [77] concluded that patients with chronic kidney disease who received liposomal doxorubicin therapy at an initial dose of 40 mg/4 weeks may require greater subsequent dose reduction, mainly secondary to mucocutaneous and hematologic toxicities.

3.4. Epirubicin

Few reports exist on the effect of renal impairment on the pharmacokinetics and safety of epirubicin. A 50% decrease in clearance was observed in patients with renal impairment, and dose reduction was recommended for these patients [75]. On the contrary, Gori *et al.* [78] concluded that weekly epirubicin appeared safe as an adjuvant chemotherapy option for early breast cancer patients with chronic renal failure undergoing hemodialysis.

3.5. Eribulin

Patients with severe and moderate renal impairment had 1.5-fold higher eribulin dose-normalized exposures compared to patients with normal renal function; there were no clinically meaningful changes in patients with mild renal impairment [79, 80]. In addition, a simulated dose reduction to 1.1 mg/m^2 eribulin in patients with moderate or severe renal impairment achieved the same exposure as 1.4 mg/m^2 in those with normal renal function [79, 80].

3.6. Etoposide

Plasma clearance of etoposide in cancer patients with renal insufficiency was lower than that in cancer patients with normal renal function [81]. A statistically significant correlation was found between etoposide clearance and creatinine clearance (CLcr). FDA label also describes that patients with impaired renal function receiving etoposide have exhibited reduced total body clearance, increased AUC and a lower volume of distribution at steady state [82].

However, some case reports and case series have demonstrated no significant difference in etoposide AUC in patients with severe renal failure who underwent hemodialysis, when compared to patients with normal kidney [83-86]. This suggests that etoposide is dialyzable, despite its high protein binding (Table **1**).

3.7. 5-Fluorouracil

Although Yeung *et al*. [87] describe in their review that reduced non-renal clearance and/or increased oral bioavailability of 5-FU was observed in a CKD patient, another report demonstrated that AUC and clearance of 5-FU in patients with renal impairment are comparable to previously published data [88]. In addition, no relationship was observed between 5-FU clearance and Scr. Another case report also showed no differences in AUC of 5-FU between a patient with end-stage renal disease (ESRD) on maintenance hemodialysis therapy and those with normal renal function [89]. These results imply there is no need for primary dose adjustment.

The results obtained by Rengelshausen *et al*. [89] also confirmed the lack of difference in AUC for the initial catabolite of 5-FU, dihydrofluorouracil, between a patient with ESRD and those with normal renal function. This suggests that the activity of dihydopyrimidine dehydrogenase was not affected by renal impairment. In contrast, the slope of the monoexponential decay of plasma concentration of 5-FU was significantly greater at 1 h than at 49 h after dialysis, and plasma clearance was correspondingly higher at 1 h than 49 h after dialysis [90]. This suggests that the plasma factors that accumulate during the interdialytic period and removed by dialysis may inhibit the activity of dihydopyrimidine dehydrogenase and consequently, fluorouracil metabolic clearance.

3.8. Irinotecan

The pharmacokinetics of irinotecan, SN-38, and SN-38G in three cancer patients with severe renal failure who were undergoing dialysis and receiving 100 mg/m^2 irinotecan as monotherapy were prospectively compared to five cancer patients with normal renal function [91]. To ensure that the subjects had similar genetic backgrounds of *UGT1A1*, only patients with *UGT1A1*1/*1*, **1/*6*, or **1/*28* were examined. The estimated terminal elimination rate constant of SN-38 in patients undergoing dialysis was approximately one-tenth of that in patients with normal renal function, resulting in a 1.7-fold increase in AUC of SN-38. Interestingly, the AUC of SN-38 based on the plasma unbound concentration (AUCu) in patients with severe renal failure was 4.38-fold higher than that in normal kidney patients [92]. This may be related to the modest but prolonged neutropenia causing a delay in the second cycle of irinotecan treatment that was observed in these patients. As SN-38 concentrations have been reported to be detectable even 500 h after administration of irinotecan in patients with normal renal function [93], a long period of exposure to relatively high concentrations of unbound SN-38 was postulated to be one of the causes of prolonged neutropenia in cancer patients with severe renal failure. Consistent with the results by Fujita *et al*. [91, 92], a cancer patient with ESRD who was undergoing hemodialysis had a lower apparent clearance of SN-38 when compared to the published values from patients with normal renal function [94]. On the other hand, de Jong *et al*. [95] demonstrated that patients with slower CLcr had a 4-fold higher risk of grade 3 or 4 neutropenia, although the pharmacokinetics of irinotecan and its metabolites did not differ from patients with the normal kidney. These results indicate that increased plasma SN-38 concentrations were found only in patients with a severe renal failure associated with a CLcr < 20 mL/min. In addition, this suggests that irinotecan is not safe in cancer patients with renal failure, even though this anticancer drug is predominantly metabolized in the liver or excreted in bile (or both).

In contrast, a phase I study demonstrated that 9 patients with moderate to severe renal failure did not appear to have increased risk of toxicity at an irinotecan dose of 225 mg/m^2 every 3 weeks [96].

3.9. Paclitaxel

To date, there are several case reports that have evaluated the effect of renal dysfunction on the pharmacokinetics and clinical response of paclitaxel. A female patient with recurrent ovarian cancer and severe renal impairment who received 3-weekly courses of paclitaxel at a dose level of 157.5 mg/m^2 showed approximately 1.5-fold higher AUC of paclitaxel than that observed in patients with normal renal function [97]. In contrast, several case studies have demonstrated no differences in the pharmacokinetics and safety of paclitaxel in ovarian cancer patients with renal impairment

requiring hemodialysis or peritoneal dialysis, when given 3-weekly paclitaxel at doses ranging from 150 to 300 mg/m^2 and carboplatin [98-101]. This indicates that combination chemotherapy consisting of paclitaxel and carboplatin is a feasible approach to improving the treatment outcome of ovarian cancer patients with chronic renal failure requiring dialysis. Pharmacokinetics and safety of weekly paclitaxel with a dose of 60-90 mg/m^2 also did not change in patients with renal failure who were undergoing hemodialysis when compared to patients with normal kidney function [98, 102, 103]. Further studies with a relatively large number of patients are warranted to elucidate the effect of renal impairment on the pharmacokinetics and safety of paclitaxel.

It should be noted that paclitaxel was not dialyzable as the peak plasma concentrations of the 300 mg/m^2 dose level before and after dialysis were almost similar [100].

3.10. Vinorelbine

To date, a limited examination of the effect of renal dysfunction on the pharmacokinetics and clinical response of vinorelbine have been performed. Based on the toxicities observed in a patient with severe renal failure who underwent hemodialysis and was treated with a dose of 25 mg/m^2 once a week, dose adjustment is suggested; no specific criteria are however advanced by dose adjustment [104].

4. CHANGES IN THE PHARMACOKINETICS AND CLINICAL RESPONSE OF TKIS ELIMINATED NON-RENALLY IN PATIENTS WITH SEVERE RENAL FAILURE

The impact of renal impairment on the pharmacokinetics and clinical response of TKIs, which are mainly disposed of by the liver, is summarized in Table **4**.

Table 4. Changes in the pharmacokinetics and clinical response of receptor TKI predominantly eliminated in feces in patients with severe renal failure.

Receptor TKIs	Renal Impairment				Note	References
	Mild	Moderate	Severe	Dialysis		
EGFR-targeting TKIs						
Afatinib		AUC, 22% ↑ (eGFR, 30-59 mL/min/1.73 m^2)	AUC, 50% ↑ (eGFR, 15-29 mL/min/1.73 m^2)	Tolerable (30 mg/body), not tolerable (40 mg/body)		[105] [106]
Erlotinib		Tolerable (CLcr, 28-37.2 mL/min)		PK, no change; Tolerable	No change in PK and tolerable (Scr, 1.6-5.0 mg/dL)	[107] [108] [109]
Gefitinib			No adverse events (CLcr, 24.3 and 25.9 mL/min)	PK, no change; safe Safe (CLcr, 34 mL/min)	Not dialyzable	[110] [111] [106]
Lapatinib					No data available	
Osimertinib				Steady state Cmax, no change (40 mg/day), Tolerable (40 and 80 mg/day)	Tolerable (Scr, 1.5 mg/dL, GFR, 26 mL/min, 80 mg/day)	[112] [113]
VEGFR-targeting TKIs (Multi receptor-targeting TKIs)						
Axitinib	CL, no change (CLcr, 60–89 mL/min)	CL, no change (CLcr, 30–59 mL/min)	CL, no change (CLcr, 15–29 mL/min)	Tolerable	CL, no change (end-stage renal disease [CLcr, < 15 mL/min]) Not dialyzable	[48] [115]

Table (4) contd….

Receptor TKIs	Renal Impairment				Note	References
	Mild	Moderate	Severe	Dialysis		
Cabozantinib	AUC, 30% ↑ (eGFR, 60-89 mL/min/1.73 m^2)	AUC, 6% ↑ (eGFR, 30-59 mL/min/1.73 m^2)				[116]
Pazopanib	CL, no change (CLcr, 30-150 mL/min)					[51]
		Safe (eGFR, 6-60 mL/min/1.73 m^2)				[118]
				Safe and tolerable		[119]
				No PK data; Safe and effective		[120, 121]
Sorafenib	PK, no Change (CLcr, 50-80 mL/min)	PK, no Change (CLcr, 30-50 mL/min)	PK, no Change (CLcr, < 30 mL/min)	No data available		[122]
	AUC, no change (CLcr, 40-59 mL/min)	AUC, no change (CLcr, 20-39 mL/min)	AUC, no change (CLcr, < 20 mL/min)	AUC, no change		[123]
				AUC, Lower; Some adverse events, but feasible	Not dialyzable	[124]
				PK, no change		[125]
				Tolerable, effective		[120, 125-132]
Sunitinib			Systemic exposure, no change	Systemic exposure, 47% ↓		[133]
			AUC of sunitinib and SU12662 (unbound), no change; Tolerable	AUC of sunitinib and SU12662 (unbound) ↓ ; Tolerable	Not dialyzable	[134]
				PK, no change		[135]
					Shorter treatment duration by toxicities (CLcr, < 60 mL/min/1.73 m^2)	[136]
				Tolerable		[120, 135, 137, 138]
Regorafenib			Mean steady-state exposure of regorafenib and active metabolites M-2 and M-5, no change (CLcr, 15-29 mL/min)			[139]
Vandetanib	AUC (unbound), 46% ↑ (CLcr, 50-80 mL/min)	AUC (unbound) 62% ↑ (CLcr, 30-50 mL/min)	AUC (unbound), 79% ↑ (CLcr, < 30 mL/min)		Dose reduction necessary (CLcr, < 50 mL/min)	[140, 141]
ALK-targeting TKIs						
Alectinib					No data available	
Ceritinib	PK, no change (CLcr, 60-90 mL/min)	PK, no change (CLcr, 30-60 mL/min)				[142]
Crizotinib	AUC of crizotinib and active metabolite, no change (CLcr, 60-89 mL/min)	AUC of crizotinib and active metabolite, no change (CLcr, 30-59 ml/min)	AUC of crizotinib and active metabolite, 79% ↑ (CLcr, <30mL/min)			[143, 144]

AUC, Area under the plasma concentration-time curve; ALK, Anaplastic lymphoma kinase; CL, Clearance; CLcr, Creatinine clearance; Cmax, Maximum plasma concentration; eGFR, Estimated glomerular filtration rate; EGFR, Epidermal growth factor receptor; GFR, Glomerular filtration rate; PK, Pharmacokinetics; Scr, Serum creatinine concentration; TKIs, Tyrosine kinase inhibitors; VEGFR, Vascular endothelial growth factor receptor

4.1. EGFR-Targeting TKIs

4.1.1. Afatinib

An open-label, the single-dose study was conducted to examine the influence of renal impairment on the pharmacokinetics of a single 40 mg dose of afatinib [105] with patients with EGFR mutation-positive advanced non-small cell lung cancer (NSCLC). The geometric mean AUCs for afatinib were 50% and 22% higher in subjects with severe and moderate renal impairment, respectively, when compared to subjects with normal renal function. In this study, afatinib was not examined in patients with eGFR <15 mL/min/1.73 m^2 or on dialysis. A case report showed that a patient with NSCLC who underwent hemodialysis tolerated 30 mg afatinib, but not up to 40 mg of the drug [106].

4.1.2. Erlotinib

NSCLC patients with renal dysfunction having elevated Scr [107] or those with chronic renal failure on hemodialysis [108] tolerated up to 150 mg/day of erlotinib and seem to have erlotinib pharmacokinetics similar to patients without renal dysfunction. Three advanced NSCLC patients who were unsuitable for chemotherapy owing to chronic renal failure received oral erlotinib at a dose of 150 mg/day; these patients well-tolerated the pharmacotherapy [109].

4.1.3. Gefitinib

The approved dose of gefitinib (250 mg/body once daily) was administered to 2 elderly patients with NSCLC affected by chronic renal failure [110]. In both patients, no severe toxicity was recorded, suggesting its possible excellent safety profile in this clinical condition. The same dose of gefitinib was safely administered to a patient with NSCLC and chronic renal failure who was undergoing hemodialysis [111]. No adverse event was observed during gefitinib administration in the patient. The pharmacokinetics of gefitinib in this patient was similar to that in patients with normal renal function. Gefitinib was also safely administered to an NSCLC patient with CLcr of 34 mL/min who was undergoing chronic dialysis [106]. Gefitinib was not eliminated by hemodialysis in this patient [111].

4.1.4. Lapatinib and Osimertinib

To date, reports on the effect of renal impairment on the pharmacokinetics and clinical outcome of lapatinib are limited. Osimertinib is a third-generation EGFR-targeting TKI that results in a high rate of response in NSCLC patients harboring acquired EGFR T790M resistance after administration of first or second-generation EGFR-targeting TKIs. The pharmacokinetics and clinical response of osimertinib were evaluated in a patient with advanced NSCLC and chronic renal failure undergoing hemodialysis [112]. The patient started osimertinib treatment from the half dose of 40 mg daily to the recommended dose. As the maximal plasma concentration of osimertinib at steady state was almost the same as those in patients with normal renal function, the dose was escalated to the recommended dose. Treatment with osimertinib 80 mg per day was well-tolerated without any adverse event. Another case report [113] also showed that 80 mg daily osimertinib was tolerated.

4.2. VEGFR-targeting TKIs (Multi Receptor-targeting TKIs)

4.2.1. Axitinib

Axitinib clearance in patients with mild and moderate renal impairment was almost similar to that in patients with normal renal function [48]. Clearance of this TKI was not substantially reduced in subjects with severe renal impairment and ESRD; however, caution should be exercised in patients with ESRD [114]. Axitinib administered to patients with metastatic renal cell carcinoma undergoing hemodialysis at a dose of 6 mg twice a day was well tolerated and allowed 12 months of disease control. Influence of hemodialysis on axitinib blood concentration was not observed [115].

4.2.2. Cabozantinib and Lenvatinib

A clinical pharmacology study was conducted to characterize the single-dose pharmacokinetics of cabozantinib in renally-impaired subjects [116]. The plasma cabozantinib AUC for impaired to normal organ function cohorts was slightly higher in subjects with mild and moderate renal impairment. No dose modification is recommended by the FDA [117]. There has been no information for lenvatinib.

4.2.3. Pazopanib

As pazopanib is excreted in urine to a very limited extent (Table **2**), no dedicated clinical trial has been performed to assess the pharmacokinetics of pazopanib in patients with impaired renal function. A population pharmacokinetic analysis revealed that CLcr values ranging from 30 to 150 mL/min did not exhibit an effect on the pazopanib clearance [51]. Kidney function did not affect the safety of the first-line pazopanib in patients with metastatic renal cell carcinoma [118]. A small cohort of ESRD patients with metastatic renal cell cancer was safely treated with pazopanib [119]. Pazopanib is also reported to be tolerable in patients on dialysis [120, 121]. No pharmacokinetic sampling in patients with severe renal impairment or those undergoing dialysis has been reported.

4.2.4. Sorafenib

Mild, moderate, and severe renal impairment do not affect the pharmacokinetics of sorafenib [122]. No significant relationships were identified between CLcr and the AUC of sorafenib or the *N*-oxide metabolite after 400 mg/body sorafenib administration [123]. According to these results, the FDA recommends that no dose adjustment is necessary [122].

Treating hemodialysis patients with sorafenib appears to be feasible without compromising clinical efficacy [124]; some severe adverse events were however recorded in these patients. Interestingly, the AUC of sorafenib in the hemodialysis patients was likely to be lower than those from the result of a phase I trial in Japanese patients with solid tumors and normal kidney function [124], although no clearance of sorafenib from plasma by the dialyzer was observed. In contrast, a study showed that the pharmacokinetic parameters of sorafenib and its active metabolite, M-2, in a patient with ESRD undergoing hemodialysis were within the reference levels observed in patients with normal renal function [125].

Several cases, case series, and retrospective studies have revealed that patients with severe renal failure who were undergoing hemodialysis were generally well tolerable to sorafenib pharmacotherapy, and some patients displayed a response [120, 125-132]. Overall, pharmacotherapy with sorafenib for patients with renal dysfunction appears to be feasible.

4.2.5. Sunitinib

Systemic exposure of sunitinib after a single oral dose was similar in patients with severe renal impairment when compared to patients with normal renal function [133]. Although sunitinib was not eliminated through hemodialysis, the sunitinib systemic exposure was 47% lower in patients with ESRD on hemodialysis compared to patients with normal renal function [133]. Consistent with these results, unbound-based AUCs of sunitinib and its active metabolite, SU12662, in subjects with severe renal impairment, with no hemodialysis required, appeared similar to subjects with normal renal function [134]. Plasma exposure to sunitinib and SU12662 appears lower in subjects with ESRD requiring dialysis when compared to subjects with normal renal function or severe renal impairment. Single-dose sunitinib 50 mg is well tolerated regardless of renal function. In contrast, the sunitinib pharmacokinetic parameters of two hemodialysis patients were within the range of the reference values reported in patients with normal renal function [135].

A retrospective study investigated the effect of renal impairment on the safety and efficacy of sunitinib [136]. No unexpected

toxicity was reported in patients with renal impairment; however, treatment was more frequently discontinued due to adverse events, and the duration of therapy (progression-free survival) was significantly shorter in these patients.

Several studies revealed that sunitinib pharmacotherapy was generally tolerable and effective even in patients with severe renal dysfunction or those who were undergoing hemodialysis [120, 135, 137, 138].

4.2.6. Regorafenib

No differences in the mean steady-state exposure of regorafenib, and its active metabolites produced mainly by hepatic CYP3A, M-2, or M-5 were observed in patients with severe renal impairment when compared to patients with normal renal function [139]. The pharmacokinetics of these compounds in cancer patients with ESRD on dialysis remains unknown.

4.2.7. Vandetanib

A renal impairment study was performed with subjects showing renal impairment according to CLcr calculated from a 24-h urine collection pre-dose of vandetanib 800 mg/body [140]. The AUC values based on unbound vandetanib were approximately 46%, 62% and 79% higher in subjects with mild, moderate, and severe renal impairment, respectively. Similar results were obtained by the FDA [141], resulting in the recommendation to reduce the starting dose to 200 mg in patients with moderate and severe renal impairment.

4.3. ALK-targeting TKIs

No information is available for the association of renal impairment and the pharmacokinetics and drug response of alectinib. Ceritinib exposures were similar between patients with mild to moderate renal impairment and patients with normal renal function, based on a population pharmacokinetic analysis [142]. No data, however, exist for patients with severe renal impairment. Population pharmacokinetic analysis for crizotinib revealed that AUC in patients with severe renal failure increased by 79% when compared to values in patients with normal kidney function [143]; mild or moderate renal impairment displayed no clinically-relevant effect [143, 144]. It is noteworthy that similar changes in AUC were observed for the active metabolite of crizotinib.

5. MECHANISMS UNDERLYING MODIFIED PHARMACOKINETICS OF NON-RENALLY ELIMINATED ANTICANCER DRUGS IN PATIENTS WITH SEVERE RENAL FAILURE

Elucidation of the underlying mechanism for the alteration of pharmacokinetics for non-renally eliminated anticancer drugs in patients with renal failure provides insights to establish strategies for the appropriate use of these therapeutic drugs in clinical practice.

In a prospective clinical pharmacological study that we performed with irinotecan [91, 92], mean AUC of SN-38 based on total plasma concentrations in the patients with severe renal failure was 1.7-fold greater than that in patients without renal failure (Table **3**); although SN-38 is mainly eliminated *via* the liver and urinary excretion of SN-38 accounts for less than 1% of the total administered dose of irinotecan [145-147]. Furthermore, the AUCu of SN-38 based on unbound plasma concentrations was approximately 4.38-fold higher in cancer patients with severe renal failure than in patients with normal kidney function [91, 92]. The unbound fraction of SN-38 was also found to be significantly (2.59-fold) higher in cancer patients with severe renal failure than in cancer patients with normal kidney function [92]. The unbound fraction of SN-38 and renal function displayed negative significant correlation, which is at least in part due to the competitive displacement of protein binding of SN-38 by a uremic toxin, 3-carboxy-4-methyl-5-propyl-2-furanpropionate (CMPF) at the site I on human albumin [92]. Fujita *et al*. [28, 92] performed mechanistic analyses to elucidate the potential mechanism(s) for the elevated AUC of SN-38 in patients with severe renal failure, and demonstrated that the hepatic uptake clearance of SN-38 decreased in such patients by 2 independent mechanisms: (1) direct inhibition of OATP1B1-mediated SN-38 uptake by uremic toxins, and (2) down-regulation of *SLCO1B1* gene expression. The saturated uptake of SN-38 by human hepatocytes was significantly inhibited by a mixture of organic anion uremic toxins including CMPF, indoxyl sulfate, hippuric acid, and indole acetate, at clinically-relevant concentrations [28]. In addition to CMPF directly inhibiting the uptake of SN-38 by hepatocytes, it inhibits those mediated by cDNA-expressed human OATP1B1. Gene expression of *SLCO1B1* in human hepatocytes was significantly down-regulated by treatment with the uremic plasma obtained from patients with severe renal dysfunction. Thus, the potential mechanism for the approximately 4.38-fold higher AUCu in cancer patients with severe renal failure than in patients with normal kidney function is considered to be the combined effects of 2 independent factors: (1) Reduced hepatic uptake of SN-38 caused by the direct inhibition by uremic toxins and down-regulation of *SLCO1B1* gene expression and (2) An increased SN-38 unbound fraction partially caused by the displacement of its protein binding by a uremic toxin, such as CMPF. Physiologically based pharmacokinetic (PBPK) modeling indicated substantially reduced the influx of SN-38 into hepatocytes and approximately one-third irinotecan dose for cancer patients with severe renal failure to produce an unbound concentration profile of SN-38 that is similar to normal kidney patients.

To generalize the findings observed in the case with SN-38, it is important to discover drugs showing similar properties to SN-38. Repaglinide is an oral hypoglycemic agent used to manage type 2 diabetes mellitus. This drug is predominantly taken up into the liver by OATP1B1, extensively metabolized by hepatic CYP3A4 and CYP2C8, and then excreted into bile *via* an ATP-binding cassette, sub-family B, member 1 (ABCB1) [148]. The total concentration base AUC of repaglinide was significantly higher in patients homozygous for *SLCO1B1* 521T>C (Val174Ala) related to reduced activity [149], suggesting that the repaglinide metabolism in the liver may be limited by the capacity of this uptake transporter. On the other hand, the AUC of repaglinide was approximately 2.7-fold greater in patients with severe renal failure (CLcr <30 mL/min) than in patients with normal kidney function [150], a result potentially caused by the decrease in OATP1B1 activity, similar to the case with SN-38. Interestingly, PBPK model analysis indicated that an approximately 52% reduction in the OATP1B1-mediated hepatic uptake clearance of repaglinide is required to correctly simulate the pharmacokinetics of the drug in subjects with severe renal failure [151]. In addition, protein binding of repaglinide to human albumin was greater than 98% [152]. These findings suggest that the unbound concentration of repaglinide may also be elevated in patients with severe renal impairment when compared to normal kidney patients.

Recently, PBPK modeling delineated potential changes in CYP2C8 or OATP1B activity in patients with renal impairment [153], as clearance of some substrates for both OATP and CYP2C8 simultaneously decreases as kidney function declines [154]. Drugs analyzed are predominantly substrates of CYP2C8 (rosiglitazone, pioglitazone), OATP1B (pitavastatin), or both (repaglinide). Pharmacokinetics of these drugs were simulated in patients with severe renal failure considering changes in glomerular filtration rate, plasma protein binding, and activity of either CYP2C8 and/or OATP1B in a stepwise manner. The PBPK analysis suggests that OATP1B activity could be decreased. Our results [28, 91, 92], and the findings of Zhao *et al*. [151] and Tan *et al*. [153] indicate that the elevated pharmacokinetic profile of drugs that are predominantly taken up by OATP1B1 into the liver in patients with renal failure is caused by reduced uptake capacity of OATP1B1. If the

reduction in hepatic uptake induced by the direct inhibition of OATP1B1 activity by uremic toxins or by suppression of *SLCO1B1* gene expression (or by both) could be quantitatively predicted, PBPK models could potentially be used to calculate the appropriate doses for cancer patients with severe renal failure, thereby obtaining AUCs similar to those observed in patients with normal kidney function.

Many anticancer drugs are predominantly metabolized by the liver CYP3A enzyme (Table **1** and **2**). The pharmacokinetics of CYP3A4/5 model drugs showed relatively smaller changes to CKD [155, 156], which is supported by the results that hepatic CYP3A activity was not affected by renal impairment-induced accumulation of plasma indoxyl sulfate [157], although uremic plasma from subjects with ESRD was reported to inhibit the metabolism of the CYP3A probe midazolam in human liver microsomes from donors with normal renal function [87]. Consistent with these results [155, 156], no effect of renal impairment on the pharmacokinetics of the anticancer drugs predominantly metabolized by the liver CYP3A was observed: (1) cytotoxic anticancer drug docetaxel (Table **3**) and (2) most TKIs, but excluding cytotoxic eribulin, etoposide and paclitaxel, and TKIs of vandetanib and crizotinib. Paclitaxel is known to be taken up into hepatocyte by OATP1B1 [32] and metabolized by CYP2C8 and CYP3A (Table **1**). Vandetanib [62] and crizotinib [42] are also substrates of OATP1B1 (Table **2**). Reduced OATP1B1-mediated hepatic uptake of these anticancer drugs in patients with renal impairment may cause increased AUC, if the OATP1B1-mediated hepatic uptake is the rate-limiting step in the overall hepatic clearance of these drugs. However, several case studies have demonstrated no differences in the pharmacokinetics and safety of paclitaxel in patients with renal impairment requiring dialysis [98-101]. This suggests the interindividual variability in the contribution of OATP1B1 and drug-metabolizing enzymes, CYP2C8 and CYP3A4, to overall hepatic elimination of paclitaxel. These hypotheses warrant future investigations.

Renal impairment is known to be associated with decreased clearance of etoposide and increased systemic exposure of eribulin. Decreased clearance of etoposide in patients with renal impairment may be caused by the relatively higher excretion rate of this anticancer drug in urine (56%) than that in feces (44%) (Table **1**). The mechanism for the increased AUC of eribulin in patients with renal failure remains unclear. However, heterotropic cooperativity induced by eribulin (substrate) and uremic toxin (inhibitor) may lead to apparent potent inhibition in CYP3A-mediated metabolism [87].

Clearance of cyclophosphamide is lower in patients with reduced renal function compared to patients with normal kidney [68, 71]. This cytotoxic anticancer drug is predominantly metabolized by the liver CYP2B6 to form the active metabolite, 4-hydroxy cyclophosphamide [10, 11]. Bupropion, which is used in smoking cessation and as an antidepressant, is also mainly metabolized by CYP2B6 [158]. Oral clearance of bupropion in subjects with impaired renal function is reported to be significantly lower than in subjects with normal kidney function [158]. These results may suggest that lower clearance of cyclophosphamide and bupropion observed in patients with renal impairment may be induced by the reduced metabolic capacity of CYP2B6 in these patients; however, further studies are warranted to clarify this proposal. At present, the mechanisms for the reduced clearance of doxorubicin, liposomal doxorubicin, and epirubicin, or increased AUC of afatinib remain unclear.

CONCLUSION

To date, a vast array of evidence for decreased clearance has been accumulated for many anticancer drugs eliminated by hepatic drug metabolism and/or transport in patients with impaired renal function. Although such alterations are clinically important especially for the anticancer drugs that frequently result in severe adverse events owing to high level of systemic exposure, the molecular basis for the effect of uremia on non-renal drug-metabolizing enzymes and transporters requires further understanding. Our results suggest that a decrease in clearance or an increase in systemic exposure of anticancer drugs in patients with renal impairment is likely to be observed for substrates of OATP1B1, which is consistent with previous findings [151, 153, 154]. Although CYP3A is responsible for the hepatic and/or intestinal metabolism of a variety of anticancer drugs, the capacity of this drug-metabolizing enzyme may not be altered in patients with renal impairment, as reported previously [156]. Systemic exposure of several, but not all substrates for both CYP3A and OATP1B1 is higher in patients with renal impairment. Hepatic uptake of these anticancer drugs by OATP1B1, but not CYP3A-mediated metabolism, may be a rate-limiting step in overall hepatic elimination, which is affected by renal function. Clarification of roles of factors such as sirtuin 1 [159-163], which is related to hepatic drug metabolism *via* CYP3A as well as kidney function, may help to elucidate underlying mechanisms. Presently, data for other drug-metabolizing enzymes and transporters especially those expressed in the canalicular membrane of hepatocytes and are responsible for biliary excretion of anticancer drugs remain limited. Thus, further *in vitro* and *in vivo* studies as well as clinical pharmacology studies in cancer patients with decreased renal failure are necessary to generate generalizable concepts, to enable the establishment of an appropriate dosing strategy of anticancer drugs. Evidently, the application of new methodologies and techniques will help us to elucidate complex details of uremic milieu on the disposition of anticancer drugs.

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