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Seizures and cancer: drug interactions of anticonvulsants with chemotherapeutic agents, tyrosine kinase inhibitors and glucocorticoids

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Patients with cancer commonly experience seizures. Combined therapy with anticonvulsant drugs (AEDs) and chemotherapeutic drugs or tyrosine kinase inhibitors carries inherent risks on drug-drug interactions (DDIs). In this review, pharmacokinetic studies of AEDs with chemotherapeutic drugs, tyrosine kinase inhibitors, and glucocorticoids are discussed, including data on maximum tolerated dose, drug clearance, elimination half-life, and organ exposure. Enzyme-inducing AEDs (EIAEDs) cause about a 2-fold to 3-fold faster clearance of concurrent chemotherapeutic drugs metabolized along the same pathway, including cyclophosphamide, irinotecan, paclitaxel, and teniposide, and up to 4-fold faster clearance with the tyrosine kinase inhibitors crizotinib, dasatinib, imatinib, and lapatinib. The use of tyrosine kinase inhibitors, particularly imatinib and crizotinib, may lead to enzyme inhibition of concurrent therapy. Many of the newer generation AEDs do not induce or inhibit drug metabolism, but they can alter enzyme activity by other drugs including AEDs, chemotherapeutics and tyrosine kinase inhibitors. Glucocorticoids can both induce and undergo metabolic change. Quantitative data on changes in drug metabolism help to apply the appropriate dose regimens. Because the large individual variability in metabolic activity increases the risks for undertreatment and/or toxicity, we advocate routine plasma drug monitoring. There are insufficient data available on the effects of tyrosine kinase inhibitors on AED metabolism.

Keywords: anticonvulsants, cancer, chemotherapeutic agents, drug interactions, epilepsy, glioma, glucocorticoids, tyrosine kinase inhibitors.

Many patients with cancer experience seizures. Two-thirds or more of patients with gliomas and one-third of patients with meningiomas have epilepsy.[1,2] For patients with systemic cancer, the overall incidence of epilepsy is higher. Seizures develop in up to 60% of patients who have a brain metastasis, depending on the primary tumor. They can also be secondary to metabolic or toxic encephalopathies, or other conditions associated with cancer.[3] As a rule, this necessitates anticonvulsant drugs to be given alongside anti-tumor therapy such as chemotherapy. Combining these therapies confers the risk of drug-drug interactions, with 6 times higher risk in brain tumors as opposed to systemic cancer.[4]

Pharmacokinetic drug-drug interactions are due to changes in absorption, distribution, metabolism, or elimination of drugs. Pharmacodynamic drug-drug interactions become manifest when drugs share characteristics related to drug-receptor binding. In daily practice, existing insights mainly relate to pharmacokinetic effects secondary to upregulation or downregulation of coenzymes belonging to the cytochrome P450 (CYP450) or UGT glucuronidation systems in the liver. Of a total of 20 CYP isoenzymes, 2C9 and 3A4 cover about 60% of all metabolic reactions.[5] These reactions are mediated by ligand-dependent nuclear receptors, including PXR (pregnane-X receptor), GC (glucocorticoid) receptor, and CAR (constitutive androstane receptor), which, after exposure to the inducing agent, are translocated into the cellular nucleus and become activated.[5] Phenytoin, phenobarbital, and carbamazepine represent enzyme inducers, mainly of 2C9, 2C19, and 3A4 together with a number of long-term metabolic effects.[6] Enzyme induction results in faster digestion of concurrently administered drugs metabolized along the same pathway, including chemotherapeutic agents, tyrosine kinase inhibitors, and glucocorticoids. Valproic acid, eslicarbazepine acetate, oxcarbazepine, perampanel, and topiramate occasionally show enzyme inhibition depending on the CYP or UGT enzymes involved, leading to toxicity of concomitant drugs, unless dose adjustment is applied.

Therapy with chemotherapeutic agents and tyrosine kinase inhibitors may similarly affect the pharmacokinetics of concurrent therapy. Both can cause enzyme induction, and tyrosine kinase inhibitors may also increase the toxicity of concurrent drugs via enzyme inhibition. Corticosteroids, probably the most commonly used drugs in neuro-oncology, can both provoke and undergo metabolic interaction. There exists large individual variability in drug metabolism depending on CYP enzyme susceptibility, age, sex, and ethnicity, all of which contribute to the risk of drug-drug interaction. An overview of the various reciprocal interactions between AEDs, chemotherapeutic drugs, tyrosine kinase inhibitors,

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and corticosteroids as reported in systemic cancer and neuro-oncology is discussed here, and these interactions are presented in quantitative terms regarding maximal tolerated dose, clearance, half-life, and area under the curve (AUC).

Methods

This review on drug-drug interactinos between AEDs and chemotherapeutics, tyrosine kinase inhibitors, and glucocorticoids is based on published articles identified via searches in PubMed, last searched in January 2015, limited to the English language. Primary sources were preferred, although occasionally review articles were used. Search terms included each of the generic names of the anticonvulsant drugs registered for focal epilepsy in adults AND "chemotherapy" OR "tyrosine kinase inhibitor" OR "corticosteroid" OR "glucocorticoid" AND/OR "interaction" OR "pharmacokinetics." Separate searches were also carried out for each of the generic names of anticonvulsant drugs registered for focal epilepsy in adults AND "glioma" OR "brain tumor" OR "cancer" AND/OR "interaction" OR "pharmacokinetics." The anticonvulsant drugs explored were clobazam, clonazepam, eslicarbazepine, gabapentin, lacosamide, lamotrigine, levetiracetam, midazolam, oxcarbazepine, perampanel, phenobarbital, phenytoin, pregabalin, retigabine, tiagabine, topiramate, valproic acid, vigabatrin, and zonisamide. Separate searches were also carried out for each of the generic names of chemotherapeutic drugs and tyrosine kinase inhibitors AND "drug interaction" AND/OR "anticonvulsant" AND/OR "pharmacokinetics." All reported clinical series on drug-drug interactions between AEDs and chemotherapeutic drugs, tyrosine kinase inhibitors, and glucocorticoids are presented. Single case reports and small series ($n < 5$) were included if no larger series were available, or if observations were relevant. For factual data on pharmacokinetic parameters of AEDs, CTDs, and TKIs as single agents representative reviews were consulted. This review has been published in a preliminary version.[7]

Results

Pharmacokinetic Characteristics of AEDs

Table 1 lists the pharmacokinetic properties of anticonvulsants indicated for the focal type of epilepsy in adults, thus also representing anticonvulsants applied for seizures associated with brain tumors or with neurological complications of systemic cancer.[8,9] Characteristics include dose, therapeutic plasma range, elimination half-life, protein binding, and clearance with and without enzyme induction.[7,10–12] In low-grade and high-grade glioma, more than 50% of patients need more than one anticonvulsant drug for seizure control, carrying risks of drug interactions.[13,14] Although newer generation AEDS have fewer enzyme-inducing effects than the classical AEDs (phenobarbital, phenytoin, carbamazepine), one does not always realize that as drug substrates they are often susceptible to the metabolic effects of other agents including AEDs. With concurrent phenytoin and carbamazepine (acting on 2C9, 2C19, 3A4), the clearance of lamotrigine, oxcarbazepine, pregabalin, tiagabine, and zonisamide becomes a factor of 1.25 to 2.0 higher, and that of clobazam 2 to 3 times higher.[15,16] Weak inducing effects can occur with the use of eslicarbazepine (3A4, UGT1A1) and lamotrigine (UGT1A4) if combined with a drug metabolized by the same co-enzymes. Weak inhibiting effects are seen with eslicarbazepine (2C9, 2C19), oxcarbazepine (2C19), perampanel (2C8, UGT1A9) and topiramate (2C19), often without much clinical impact.[11] Valproic acid is a enzyme inhibitor (UGT1A4), causing a doubling of the AUC of lamotrigine.[17] All these agents are mainly metabolized by the liver. High protein-binding drugs such as phenytoin and valproic acid, and benzodiazepines including clobazam, clonazepam, and midazolam, may cause drug-drug interactions because of competition for binding with other strongly protein-linked agents. Gabapentin, levetiracetam, lacosamide, pregabaline, and vigabatrin are mainly renally eliminated, and thus much less involved in drug interactions. For further details on reciprocal interactions between AEDs, we refer to other reviews.[10,11,15,18,19] Table 2 lists for each of the anticonvulsants, the co-enzymes responsible for substrate metabolism and enzymes that become induced or inhibited in their metabolic activity.[11,12,15,16,20]

Influence of AEDs on Chemotherapeutic Drug Activity

Table 3 provides pharmacokinetic data on the effect of AEDs on the metabolism of chemotherapeutic drugs.[21–54] We discuss here the more complicated metabolic changes of chemotherapeutic drugs with AEDs. Lomustine (CCNU) and carmustine (BCNU, applied with Gliadel wafers) are alkylating agents frequently used to treat gliomas, either as single agents, as part of the PCV (procarbazine, CCNU, vincristine) regimen, or together with bevacizumab. Although experimental data indicate enhanced metabolism of these nitrosoureas with phenobarbital, there are no pharmacokinetic data available on humans using concomitant EIAEDs.[46,47] Lomustine together with valproic acid may cause hematological toxicity due to independent yet additive effects of both agents on the bone marrow.[55,56]

Cyclophosphamide is applied in malignant lymphoma, leukemia, and in carcinoma of ovary, breast, endometrium, and lung, and often coadministered with thiotepa. When cyclophosphamide is metabolized, it is converted into the active metabolite 4-hydroxycyclophosphamide.[23,57] Concurrent therapy with the enzyme inducers carbamazepine or phenytoin yields smaller peak concentrations, increased clearance, and diminished AUC of cyclophosphamide, alongside higher peak concentrations and larger AUC of 4-hydroxycyclophosphamide.[23,25] These observations illustrate that in case of coenzyme-dependent conversion of a parent drug into the active metabolite, a concurrently administered enzyme inducer produces enhanced effects of the parent drug despite acceleration of its own metabolism.

Thiotepa is an alkylating agent applied in bladder cancer and malignant lymphoma, and metabolized into its active metabolite tepa. Tepa shows a longer elimination half-life than thiotepa and similar pharmacological properties.[24] Concurrent thiotepa and carbamazepine or phenytoin result in accelerated clearance of the primary drug, and organ exposure to tepa is increased by a factor of 2.[24,25] The use of vincristine with carbamazepine or phenytoin results in a substantially shorter elimination half-life and smaller AUC.[27]

Methotrexate, particularly high-dose methotrexate, is an essential part of chemotherapy for leukemia and non-Hodgkin's lymphoma, including CNS lymphoma. In children with acute leukemia, combining methotrexate with EIAEDs was associated with worse survival (HR=2.7) and faster clearance of methotrexate

Table 1. Pharmacokinetic characteristics of antiepileptic drugs[a]

AED	Usual Oral Dose (mg/day)	Therapeutic Range (mg/L)	Oral Bioavailability (%)	Time to Steady State (days)	$T_{1/2}$ (h) without Enzyme Inducers	$T_{1/2}$ (h) with Enzyme Inducers	Cl (mL/kg/h) without Enzyme Inducers	Cl (mL/kg/h) with Enzyme Inducers	Protein Binding (%)
Carbamazepine	400–1600	4–12	75–85	2–4	8–20	9–10	133	80	75
Clobazam	5–40	0.1–0.3	80–90	10–30	10–45	12–60	40–70	[b]factor 2–3	85
Clonazepam[c]	0.5–4, max.20	0.02–0.08	90	17–56	1–4	1–3	90	factor 1.2–1.6	85
Eslicarbazepine	400–1200	3–35	90	3–4	20–24	9–20	35–50	40–65	40
Gabapentin	900–3600	12–20	<60	1–2	5–9	5–9	120–230	120–230	0
Lacosamide	200–400	10–20	>95	3	12–16	12–16	28–40	28–40	<15
Lamotrigine	200–600	2.5–15	>95	3–15	22–38	14–15	20–35	50–80	55
Levetiracetam	1000–3000	8–26	80–90	1–2	5–11	5–8	30–50	45–75	0
Midazolam[d]	in 5–15	100–400	30–70	1–2	1–4	1–2	250–540	12–30	95–97
Oxcarbazepine	900–2400	12–35	80–100	2–3	5–30	6–19	40–50	50–70	40–60
Perampanel	4–12	0.2–1.0	100	10–19	66–105	∼25	8–12	12–20	95%
Phenobarbital	30–180	10–40	95	15–30	70–140	80–100	6–9	12–18	45–60
Phenytoin	150–400	10–20	95	6–21	24–100	<24–72	7–42	factor ∼2	85–95
Pregabalin	150–600	2–8	90	1–2	5–7	5–7	45–75	45–75	0
Retigabine	600–1200	–	60	1–2	6–10	4–7	670	470	80
Topiramate	100–500	5–20	81%–95%	4–7	20–30	9–12	15–36	30–50	15
Valproic acid	500–2500	50–100	>95	2–4	13–18	2–11	6–15	4–10	85–95
Vigabatrin	200–300	0.8–36	80–90	1–2	6–8	4–6	130–150	130–150	0
Zonisamide	200–600	10–38	>90	5–12	50–70	25–37	15–20	20–30	40–60

Abbreviations: AED, antiepileptic drug; Cl, clearance; in, intranasal.
[a]Data drawn from Johannessen SI, 2006[10]; Bénit CP, 2012[7]; Patsalos, 2013[11]; De Leon, 2013[16]; Italiano D, 2013.[12]
[b]Despite faster clearance, clinical activity of clobazam is 1.5 to 2 times higher due to increased conversion into the active metabolite N-desmethylclobazam.
[c]Use of clonazepam as oral or buccal (sublingual/sublabial) administration.
[d]Midazolam as intranasal administration on an as-needed basis.

Table 2. Metabolism of antiepileptic drugs

AED	Metabolism	Active Metabolite	Substrate (CYP)	Inducer (CYP)	Inhibitor (CYP)
Carbamazepine	CYP450	Carbamazepine epoxide	CYP3A4, 1A2, 2C8, 2C9, 2C19	CYP 1A2, 2A6, 2B6, 2C9, CYP 2C19, 3A4, UGT1A1, 2B7, 2B15, epoxide hydrolase	–
Clobazam	CYP450	N-desmethylclobazam	CYP3A4, 2C19 (2B6)	CYP3A4, UGT 1A1	CYP2C19, 2D6, UGT1A4, 1A6, 2B4
Clonazepam	CYP450		3A4	–	–
Eslicarbazepine	CYP450, 1/3 by UGT	S-licarbazine	UGT 1A4, UGT 1A9 (2B4, 287, 2B17)	CYP3A4, UGT 1A1, 3A4	2C9, 2C19
Gabapentin	Not metabolized		–	–	–
Lacosamide	CYP 450, 40% via renal excretion		CYP2C19 (2C9, 3A4)	–	–
Lamotrigine	75% via UGT		UGT 1A4 (1A1, 1A9, 2B7)	UGTs	–
Levetiracetam	Hydrolysis in blood, 66% via renal excretion		–	–	–
Midazolam	CYP450		3A4, 2C19, 2B6		3A4
Oxcarbazepine	Glucuronide conjugation, mainly via renal excretion	10-hydroxycarbazepine	UGTs, arylketone reductase	CYP3A4, UGT1A4	CYP2C9, 2C19
Perampanel	CYP450, UGT		3A4, 3A5	2B6, 3A4/5	2C8, 1A9
Phenobarbital	CYP450		CYP2C9 (2C19, 2E1)	CYP1A2, 2B6, 2C9, 2C19, 2E1, 3A4, UGT1A1	–
Phenytoin	CYP450		CYP2C9, 2C19	CYP1A2, 2B6, 2C8, 2C9, 2C19, CYP 3A4, epoxide hydrolase	–
Pregabalin	Not metabolized		–	–	–
Retigabine	UGTs, N-methylation, 30% via renal excretion, CYP 450		UGT 1A4 (1A1, 1A3,1A9)		
Topiramate	CYP450, UGT, 40% via renal excretion			3A4, UGT1A4, beta-oxidation	2C19
Valproic acid	CYP450, UGT, β-oxidation		UGT 1A3, 2B7 CYP 2A6, 2C9, 2C19, 2B6	–	CYP2C9, UGT1A4, UGT2B7, epoxide hydrolase
Vigabatrine	70% via renal excretion		–	2C9	2C19
Zonisamide	CYP450		CYP3A4 (2C19, 3A5)		2C19

Abbreviation: CYP, cytochrome P450 enzyme.
CYP or UGT co-enzymes within brackets in the Substrate column indicate that these are lesser involved in the metabolism of corresponding AEDs.
Data drawn from Vecht CJ, 2003[20]; Johannessen Landmark C, 2012[15]; Patsalos PN. 2013[11]; Italiano D, 2013[12]; De Leon J, 2013.[16]

Table 3. Influence of interfering antiepileptic drugs (AEDs) on affecting the activity of chemotherapeutic drugs (CTD)

Group of CTD	CTD	Interfering AEDs	Mechanism of Metabolism			No of Pts	MTD of CTD	Change in CTD Activity	Factor of Change in Metabolism	Reference
			Substrate (CYP)	Inducer (CYP)	Inhibitor (CYP)					
Alkylating agents	Busulfan	PHT	Glutathione conjugation			43		Cl ↑ T 1/2 ↓ AUC ↓	1.21 0.84 0.61	Hassan, 1993[21] Carreras, 2010[22]
	Cyclophosphamide Active metabolite: 4-hydroxycycloph.	PHT CBZ PHT CBZ PB experimental	2A6, 2B6, 2C9, 2C18 2C19; 3A4, 3A5 30%–60% by renal elimination	2C8		14 1 14 1		Cl ↑ T 1/2 ↓ AUC ↓ AUC ↓ C max ↓ AUC ↑ AUC ↑	2.1 0.45 0.41 0.60 0.81 1.58 1.29–1.51	Slattery, 1996[23] De Jonge, 2005[24] Ekhart 2009[25]
	Procarbazine	EIAEDs				49	nEI 334 mg/m^2 EI 393 mg/m^2	C max ↓	0.72	Grossman, 2006[60]
	Lomustine	PB	3A4		2C11	–				Chang, 1994[46] Levin, 1979[47]
	Temozolomide	None	–	–	–	15		–	–	Gilbert, 2007[44] Maschio, 2008[45]
	Thiotepa. Activ. metabolite:Tepa	CBZ, PHT	2B6, 3A4			1 1		AUC ↓ AUC ↑	0.49–0.57 1.74–2.15	De Jonge, 2005[24] Ekhart, 2009[25]
Vinca alkaloids (Mitotic spindle inhibitors)	Vincristine (as part of PCV)	PHT, CBZ	3A4			15		Cl ↑ T 1/2 ↓ AUC ↓	1.63 0.65 0.57	Bollini, 1983[26] Villikka, 1999[27]
Taxanes (Microtubule agents)	Docetaxel	EIAEDs	3A4					Cl ↑		Chang, 1998[29]
	Paclitaxel	EIAEDs	2C8, 3A4	2C8		25	nEI 140–240 mg/m^2 EI 200–360 mg/m^2	Cl ↑ Dose↑ Css = at MTD	2.05 43.7 nM 46.2 nM	Chang, 1998[29] Fetell, 1997[30]
Anti-metabolites	MTX, HD-MTX	EIAEDs				42 45	HD 1–8 gr/m^2	AUC ↓	0.58	Relling, 2000[31] Ferreri, 2004[32]
		Levetiracetam	Tubular excretion			2	HD 12 gr/m^2	Cl ↓ T 1/2 ↑	1.7 1.4	Bain, 2014[33]

Continued

Table 3. *Continued*

Group of CTD	CTD	Interfering AEDs	Mechanism of Metabolism			No of Pts	MTD of CTD	Change in CTD Activity	Factor of Change in Metabolism	Reference
			Substrate (CYP)	Inducer (CYP)	Inhibitor (CYP)					
Camptothecin derivatives (Topo-isomerase I inhibitors)	Irinotecan (CPT-11). Active metabolite: SN-38	EIAEDs	3A4, 1A1	3A4		32	nEI: 117–350 mg/m^2 [a]	Cl ↑	1.99–2.34	Minami 1999[34]
		Non-EIAEDs				9	EI: 411–750 mg/m^2	T 1/2 =	=	Gilbert, 2003[35]
		VPA				53	nEI: 350–400 mg/m^2 [b]	AUC ↓	0.26–0.74	Prados, 2006[36]
						32	EI: 750 mg/m^2		1.82–2.06	Jaeckle, 2010[37]
						46	nEI + TMZ: 200 mg/m^2	Cl	=	Loghin, 2007[38]
						46	EI + TMZ: 500 mg/m^2 [c]	T 1/2	=	De Jong, 2007[39]
							SN-38	T 1/2	=	
								AUC ↓	0.58	
								Cl ↑	1.28	
								AUC ↓	0.59	
	Topotecan	PHT				1		Cl ↑	1.45–1.47	Zamboni, 1998[40]
								AUC ↓	0.40	
Podophyllotoxin derivatives (Topo-isomerase II inhibitors)	Etoposide	EIAEDs	3A4			29		Cl ↑	1.44–1.77	Rodman, 1994[41]
						17		AUC ↓	0.63	Mross, 1994[42]
	Teniposide					6		Cl ↑	1.93–2.46	Baker, 1992[43]
						42				Relling, 2000[31]

Abbreviations: bid, bis in die; CBZ, carbamazepine; EIAEDs, enzyme-inducing antiepileptic drugs; PB, phenobarbital; PCV: procarbazine, CCNU, vincristine; PHT, phenytoin; VPA, valproic acid; Cl, clearance; T 1/2, Plasma drug elimination half-life; AUC, area under time-concentration curve; MTD, maximum tolerated dose; nEI, MTD without EIAEDs; EI, MTD with EIAEDs and corresponding Cl, T 1/2, or AUC.

[a]Scheme Gilbert, 2003[35]: 90-min i.v. infusion once weekly for 4 out of 6 weeks (as single agent).

[b]Scheme Prados, 2006[36]: 350 mg/m^2 i.v. every 3 weeks or 750 mg/m^2 with EIAEDs (as single agent).

[c]Scheme Loghin 2007[38]; nEI: 200 mg together with temozolomide 150 mg/m^2 days 1–5 q 28 days, and i.v. irinotecan on days 1 & 15 of each cycle, vs EI: 350–550 mg/m^2 with similar doses temozolomide/irinotecan.

and teniposide.[31] Pharmacokinetic studies in primary CNS lymphoma show that methotrexate and concurrent EIAEDs result in half the AUC, possibly depending on altered aldehyde oxidase activity.[32] Alternatively, EIAEDs may lead to reduced cellular uptake of methotrexate secondary to diminished intracellular folate carrier activity.[58] Based on these observations, one might be inclined to prescribe a noninteracting AED like levetiracetam. However, a potential source of interaction between high-dose methotrexate and levetiracetam is competition for tubular excretion. This leads to a 1.7 lower clearance of methotrexate and patients show signs of hypertension and renal failure.[33,59]

Camptothecin derivatives are topoisomerase-I inhibitors, including irinotecan (CPT-11), 9-aminocamptothecin (9-AC), and topotecan. Irinotecan is applied in colorectal cancer and malignant glioma, and is transformed by 2C8 and 3A4 into the active metabolite SN-38 (7-ethyl-10-hydroxy camptothecin) via a carboxylesterase. Subsequently, SN-38 is glucuronidated by UGT1A1.[38] With concurrent EIAEDs, the clearance of irinotecan rises and its maximum tolerated dose becomes 3.5 times higher.[35–37] Combination therapy of valproic acid with irinotecan results unexpectedly in a 41% lower systemic exposure to SN-38, possibly caused by altered protein binding.[39] The clearance of 9-AC doubles if combined with EIAEDs.[34] Topotecan with phenytoin results in a faster clearance (factor 1.45) and smaller systemic exposure (factor 0.45).[40] Also, leucopenia, neutropenia, and thrombopenia occur in 71% with concomitant EIAEDs as opposed to 59% with non-EIAEDs, which is difficult to explain.[34] The topoisomerase II inhibitors etoposide and teniposide are mainly applied in lung and ovarian cancer, and are susceptible to the effects of concurrent enzyme inducers. Use of phenobarbital or phenytoin leads to a 3-fold increase of the clearance of tenoposide.[41,43]

Influence of Chemotherapeutic Drugs on AED Activity

Table 4 provides pharmacokinetic data on the effect of chemotherapeutic drugs on the metabolism of AEDs, leading to either diminished antiseizure activity or increased toxicity of AEDs.[48–63]

Procarbazine (PCN) is one of the few chemotherapeutic agents that inhibits the 2C and 3A coenzymes, particularly on a prolonged dosing schedule when signs of hepatotoxicity may occur, partly due to autoinhibition of its own metabolism. These effects are only seen with PCN as single agent at doses approaching the maximum tolerated dose (350–400 mg/m^2), and not at a conventional single daily dose of 150 mg/m^2 or at doses as low as 60 mg/m^2 as part of the PCV regimen.[60] The inhibiting effects of PCN on the pharmacokinetics of 3A4 substrate drugs possibly explain frequent skin hypersensitivity related to AED plasma levels.[61] There are no signs that EIAEDs affect the pharmacokinetics of procarbazine.[60]

Cisplatin leads to 50% lower plasma levels of phenytoin, carbamazepine and valproic acid, probably based on a combination of lesser intestinal absorption and protein displacement.[28,48,49] Impairment of absorption by vinblastine also results in lower plasma levels of these AEDs.[26,53]

High-dose methotrexate may lower plasma concentrations and induces faster clearance of concomitant phenytoin by both diminished gastrointestinal absorption and folic acid rescue.[26] Rapid decline of serum valproate concentrations during high-dose methotrexate treatment can be explained by competition for albumin binding as larger proportions of unbound valproic acid become available for liver breakdown. The routine alkalization during methotrexate infusion increases its renal elimination together with enhanced excretion of valproic acid.[54] The pyrimidine antagonists 5-fluorouracil, doxifluridine, and the prodrug capecitabine applied in colorectal cancer are 2C9 inhibitors, leading to 2-fold to 4-fold higher plasma levels of phenytoin and phenobarbital.[51,52,62]

Interactions With Tyrosine Kinase Inhibitors and Other Targeted Agents

Table 5 presents pharmacokinetic data on drug-drug interactions between anticonvulsants and tyrosine kinase inhibitors or other targeted agents.[36,63–91]

Table 4. Influence of interfering chemotherapeutic drug (CTD) on affecting antiepileptic drug (AED) activity

AED	CTD	CTD/dose	Involved Mechanism	No. of Pateints	Change in AED Activity	Factor of Change	Reference
Phenytoin Carbamazepine	Cisplatin	20 mg/m^2	Protein displacement/ diminished absorption	1	Cl ↑	2.29	Neef, 1988[48] Grossman, 1989[49] Dofferhof, 1990[50]
Phenytoin	CCNU Cisplatin	40 mg/m^2 40 mg/m^2		17	Dose ↑	1,39	
Phenytoin	Carboplatin	400 mg/m^2		1	Dose ↑	1.21	
Phenytoin	5-Fluorouracil	370–425 mg/m^2	2C9 inhibition	2	Dose ↓	0.53–0.72	Brickell, 2003[51]
	Capecitabine			1	Dose ↓	0.46	Konishi, 2002[62]
	Doxifluridine	800 mg/d		1	Plasma level ↑	4	Privitera, 2011[52]
Phenytoin	Tamoxifen		3A, 2C19, 2D6	1	Dose ↑	1.16	Rabinowicz 1995[53]
Valproic acid	Cisplatin	30 mg/day (with BEP regimen)	Protein displacement/ diminished absorption		Plasma level ↓	0.5	Neef, 1988[48] Ikeda, 2005[28]
Valproic acid	Methotrexate	1 g/m^2		1	Plasma level ↓	0.25	Schroder, 1994[54]
Phenytoine	Vinblastine	10 mg	Diminished Absorption	1	Plasma level ↓	0.59	Bollini, 1983[26]

Table 5. Influence of interfering antiepileptic drug (AED) on affecting activity of tyrosine kinase inhibitors and other targeted agents

Tyrosine Kinase Inhibitor	Mechanism (Target)	AED and Dose	Involved CYPs/UGTs			No of Patients	Dose at MTD	Change in CTD Activity	Factor of Change of Metab	Reference
			Substrate	Inducer	Inhibitor					
Bortezomib	Proteasome inhibitor	EIAEDS	CYP3A (2C19)			3	nEI + TMZ 1.3 mg/m^2 EI + TMZ ?	Cl ↑ AUC ↓	2.75 0.54	Portnow, 2012[63]
Crizotinib	ALK/MET/ROS1 inhibitor	Midazolam	CYP3A4 (1A9, 2D6, 2C19)	CYP2B6, 2C8, 2C9, UGT	CYP3A4			AUC ↑	3.7	Mao, 2013[64]
Dasatinb	SCR, Bcr-Abl,	EIAEDs	CYP3A (2C8, UGT)		CYP3A4, 2C8, 1A1			AUC ↓	0.45	Reardon, 2012[65]
Enzastaurin	PI3 K/AKT	EIAEDs	CYP3A (2C19)			15	nEI 525 mg	Cl ↑ AUC ↓	6.96 0.21	Kreisl, 2010[66]
Erlotinib	EGFR	EIAEDs Midazolam	CYP3A (1A1, 1A2, 2C8, 2D6)	CYP3A4		90 110	nEI + TMZ 150 mg/d nEI 200 mg/d EI + TMZ 450 mg/d EI 500 mg/d	AUC ↓ AUC ↓	0.45–0.63 0.76	Prados, 2006[92] Vd Bent, 2009[67] Shao, 2014[68]
Gefitinib	EGFR	EIAEDs	CYP3A, 2D6 (1A1, 2C19)		2C19, 2D6	68 30	nEI + TMZ 250 mg/d EI + TMZ 1000 mg/d	Cl ↑ T 1/2 ↓ AUC ↓	2.27–3.42 0.84 0.31–0.71	Reardon, 2006[69] Prados, 2008[70]
Imatinib	Bcr-Abl, c-kit, PDGFR	EIAEDs	CYP3A (2C9, 2D6)	3A4, 2C8	3A4/5, 2C9, 2D6	33	nEI 1200 mg/d EI 1200 mg/d nEI + TMZ 1000 mg/d EI + TMZ 1000 mg/d	Cl ↑ T 1/2 ↓ AUC ↓ Cl ↑ T 1/2 ↓ AUC ↓	3.42–4.13 0.30–0.60 0.26–0.79 1.30 0.39 0.76	Reardon, 2008[71] Wen, 2006[72] Pursche, 2008[73]
		Levetiracetam Valproic acid Lamotrigine Phenytoin Carbamazepine Oxcarbazepine Topiramate						Through Plasma levels	0.97 1.02 1.01 0.31 0.29 0.45 0.58	
Lapatinib	EGFR, HER2	CBZ Midazolam	CYP3A (1A2, 2C8, 2C9, 2C19, 2D6)		3A4, 2C8	16 24	EI 1000 mg	Cl ↑ T 1/2 ↓ AUC ↓ AUC ↑	8.83 0.28 0.27–0.28 1.4	Smith, 2009[75] Thiessen, 2010[74] Shao, 2014[68]
Pazopanib	c-kit, FGFR, PDGFR, VEGFR1–3	EIAEDs Midazolam	CYP3A (1A2, 2C8)	3A4	CYP3A4, 2D6 2B6, 2C9, 2C19	75		AUC ↓ AUC ↑	~0.5 1.35	Reardon, 2013[76] Shao, 2014[68]

Continued

Table 5. *Continued*

Tyrosine Kinase Inhibitor	Mechanism (Target)	AED and Dose	Involved CYPs/UGTs			No of Patients	Dose at MTD	Change in CTD Activity	Factor of Change of Metab	Reference
			Substrate	Inducer	Inhibitor					
Evorolimus	mTOR	EIAEDs	CYP3A (2C19)			32		AUC ↓	0.48	Mason, 2012[77]
Sirolimus	mTOR	EIAEDs	CYP3A (2C19)			23		T 1/2 ↓	0.46–0.75	Boni, 2007[78]
						25		AUC ↓	0.54–0.62	Kuhn, 2007[79]
						36				Galanis, 2011[80]
Temsirolimus	mTOR	EIAEDs	CYP3A (2C19)			25	nEI 170 mg/d	Cl ↑	1.20–1.47	Boni, 2007[78]
		Valproic acid				36	EI 250 mg/d	T 1/2 =		Kuhn, 2007[79]
						8		AUC ↓	0.66–0.85	Galanis, 2005[80]
								C max	~ 2	Coulter, 2013[81]
Sorafenib	c-kit, PDGFR, RAF, VEGFR1-3	EIAEDs Midazolam	CYP3A, UGT1A9		CYP3A4, 2B6, 2C8, 2C9, 2D6, UGT1A1, 1A9	32		T1/2 ↓	0.39–0.56	Reardon, 2011[82]
								AUC ↓	0.36–0.49	Flaherty, 2011[83]
								AUC ↓	0.85	
Sunitinib	PDGFR, VEGFR, c-KIT	EIAEDs	CYP3A (2C19)							Widmer, 2014[86]
										Bilbao, 2015[84]
Tamoxifen	Estrogene receptor	Phenytoin	CYP3A (2C19)			1		Dose ↓	0.46	Gryn, 2014[85]
Tipifarnib	Ras, Farnesyl-TF inhibitor	EIAEDs	CYP3A (2C19)				nEI 300 mg bid EI 600 mg bid	Cl ↑ T 1/2 = AUC ↓	2.90 = 0.52	Cloughesy, 2005[87]
Vandetanib	EGFR, RET, VEGFR2	EIAEDS	CYP3A		CYP2D6	79		Cl = T 1/2 = AUC =		Kreisl, 2012[88]
Vatalanib	C-kit, PDFGR VEGFR1-3	EIAEDs	CYP3A (2C19)			10	nEI 1000 mg bid EI 1000 mg bid	Cl ↑ T 1/2 = AUC ↓	2.68–3.09 0.42–0.82	Reardon, 2009[89] Gerstner, 2011[90]
Vemurafenib	V600E BRAF kinase		CYP3A4	CYP3A4	CYP1A2, 2D6					Da Rocha Dias, 2013[91]

Abbreviations: bid, bis in die; CBZ, carbamazepine; EIAEDs, enzyme-inducing anti-epileptic drugs; PB, phenobarbital; PCV: procarbazine, CCNU, vincristine; PHT, phenytoin; VPA, valproic acid; Cl, clearance; T 1/2, plasma drug elimination half-life; AUC, area under time-concentration curve; MTD, maximum tolerated dose; nEI, MTD without EIAEDs; EI, MTD with EIAEDs and corresponding Cl, T 1/2, or AUC.

A number of tyrosine kinase inhibitors have been tested in phase 1 and 2 trials for gliomas, and many of these trials also examined pharmacokinetics with concurrent EIAEDs and non-EIAEDs. When combined with 3A4-inducing AEDs, tyrosine kinase inhibitors usually have a 2-fold higher clearance rate and corresponding reduction of AUC. Crizotinib, dasatinib, imatinib, and lapatinib particularly show substantially faster metabolism with concurrent EIAEDs.[64,65,72–78,92] For imatinib and lapatinib, organ exposure is about 4 times lower without dose adjustment, representing a moderate drug interaction. Drug interactions are defined as strong if they produce a larger than 5-fold change in metabolism, moderate as 2-fold to 5-fold, and mild if between 1.25-fold and 2-fold.[68] Some tyrosine kinase inhibitors are 3A4 inhibitors with inherent risks of toxicity when combined with other 3A4 substrate drugs. Examples of a higher organ exposure of combined drugs are that of crizotinib with midazolam by a factor 3.7, of imatinib with simvastatin by a factor 3.5, and sorafenib with docetaxel by a factor 1.5 to 1.8.[64,68] One may expect to see similar changes in metabolism with other 3A4 substrate drugs including both older and newer generation AEDs. Until now, however, hardly any data on the effect of TKIs on AED metabolism are available. For pharmacokinetic characteristics of individual tyrosine kinase inhibitors, we refer to other reviews.[68,93–95]

Temsirolimus (CCI-779) is an ester of sirolimus (rapamycin) inhibiting the mTOR protein, which regulates key molecules of the PI3K and AKT pathway. mTOR blockers are applied in renal cell carcinoma, tuberous sclerosis, and subependymal giant cell astrocytomas, and has been tested as phase II drug in glioblastoma.[78–80] Combined use with EIAEDS produces a diminished systemic exposure to temsirolimus by a factor of 0.66 to 0.85, to everolimus by a factor of 0.48, and to sirolimus by a factor of 0.54 to 0.62.[77,79] Valproic acid reduces the maximum tolerated dose of temsirolimus to 35 mg/m^2 in adults and to 150 mg/m^2 in children, possibly due to inhibition of CYP3A4.[81] A dose as low as 25 mg/m^2 is sufficient to reduce mTOR activity.[81]

Interactions With Glucocorticoids

Glucocorticoids are frequently applied in cancer for multiple reasons, and in neuro-oncology mainly to control tumor-induced brain edema. Glucocorticoids can influence the activity of a number of CYP coenzymes including 3A4, 3A5, and to a smaller extent 2C8, 2C9, and C19 by activation of the nuclear GC receptor. GCs control transcription of a wide spectrum of genes, including *3A5* and *2C9*. Corticosteroids are mainly 3A4 enzyme inducers. In this way, they influence the pharmacokinetics of concurrent drugs, although clinical studies on interactions between steroids and AEDs are relatively scarce. (Table 6)[96–101] A clinically relevant dose of 16 mg/day of dexamethasone increases 3A4 activity by 25%, but there is substantial individual variability ranging from no increase to a 49% to 70% increase in one-third of patients.[100] This explains observations of faster clearance and subtherapeutic levels of phenytoin with concurrent dexamethasone.[99] Increasing phenytoin dosing by a factor of 1.5 to 2.0 is necessary to maintain therapeutic plasma levels. After upward dose adjustment of phenytoin with concurrent steroids, and once arriving at the stage of steroid tapering, phenytoin concentrations can easily rise to toxic levels if it is not also tapered.[101] However, increased phenytoin levels occur occasionally in combination with dexamethasone, which has been explained by competition for enzyme-binding. These observations underscore the possibility of unexpected drug-drug interactions.[20,102]

Concurrent carbamazepine, phenytoin, and phenobarbital lead to faster metabolism of methylprednisolone, prednisolone, and dexamethasone.[96,97] The inducing effects of phenytoin on the clearance of dexamethasone vary between a factor of 3 up to 12 with a correspondingly low AUC of 0.13.[96,103] Phenytoin together with prednisone or prednisolone results in a faster

Table 6. Influence of antiepileptic drugs (AEDs) on corticosteroid activity

AED	Steroid	No. of Patients	Change in Steroid Activity	Factor of Change	Reference
Carbamazepine	Prednisolone	6	Cl ↑	1.41	Bartoszek, 1987[96]
			T 1/2 ↓	0.64	
Phenobarbital		6	Cl ↑	1.79	Bartoszek, 1987[96]
			T 1/2 ↓	0.44	
Phenytoin		2	Cl ↑	1.77	Bartoszek, 1987[96]
			T 1/2 ↓	0.71	
Carbamazepine	Methylprednisolone	5	Cl ↑	3.09	Bartoszek, 1987[96]
			T 1/2 ↓	0.46	
Phenobarbital		5	Cl ↑	4.42	Bartoszek, 1987[96]
			T 1/2 ↓	0.46	
Phenytoin		2	Cl ↑	5.79	Bartoszek, 1987[96]
			T 1/2 ↓	0.29	
Phenytoin	Dexamethasone	15	Cl ↑	2.93	Chalk, 1984[97]
			T 1/2 ↓	0.54	
Phenytoin		6	Plasma Conc ↓	0.5	Wong, 1985[98]

Abbreviations: bid, bis in die; CBZ, carbamazepine; EIAEDs, enzyme-inducing anti-epileptic drugs; PB, phenobarbital; PCV: procarbazine, CCNU, vincristine; PHT, phenytoin; VPA, valproic acid; Cl, clearance; T $\frac{1}{2}$, plasma drug elimination half-life; AUC, area under time-concentration curve; MTD, maximum tolerated dose; nEI, MTD without EIAEDs; EI, MTD with EIAEDs and corresponding Cl, T $\frac{1}{2}$, or AUC.

clearance of steroids by a factor of 1.5. Overall, the plasma half-life of steroids shortens to about half its original value with concurrent EIAEDs. The biological half-life as being more decisive for the duration of clinical activity of glucocorticoids is probably not or much less affected. During cancer treatment, corticosteroids are usually prescribed at supratherapeutic doses, which may explain why signs of insufficient steroid dosing often remain undetected.

Discussion

Epilepsy occurs frequently in cancer, particularly with gliomas, meningiomas, and brain metastasis.[1–3] In general, patients undergo intensive therapy, including surgery, radiation therapy, and one or more lines of chemotherapy. In parallel, patients will receive antiepileptic drugs and almost all need steroids at some stage of their disease. Not surprisingly, this setting carries a high risk for drug-drug interactions.[4] As antineoplastic drugs often have a narrow therapeutic window close to the maximum tolerated dose, these interactions can easily result in insufficient antitumor therapy or in drug toxicity. This may have a major clinical impact, as illustrated by observations of shorter survival in children with acute lymphoblastic leukemia receiving concurrent EIAEDs.[31] Temozolomide and bevacizumab are probably the most frequently applied antitumor agents in neuro-oncology, although neither are subject to known drug-drug interactions.[44,45] However, hematological toxicity associated with chemotherapeutics, including temozolomide, may be aggravated by direct toxic effects of valproic acid on the bone marrow.[55,104] In cases of combined temozolomide and valproic acid, multifactorial analysis indicates that the former is decisive for developing thrombopenia.[105,106] Recently, valproic acid is under study as an anti-tumor agent based on ability to block the histone deacetylase enzyme. Clinical application of valproic acid as a histone deacetylase I and II blocker, particularly combined with DNA-targeting chemotherapy, has shown promising results in glioblastoma and other cancers.[14,104,107]

The large majority of chemotherapies and tyrosine kinase inhibitors are susceptible to or may induce drug-drug interactions. In order to apply proper drug regimens, phase 1/2 trials testing new agents against glioma often include separate arms with and without EIAEDs, providing data on corresponding maximum tolerated dose, clearance, half-life, and AUC (see Tables 3–5). Despite this body of information, we hardly know to what extent standardized dose adjustment is applied in the daily practice of cancer treatment. Likewise, in cases of tumor progression, it may be unclear if the progression is caused by insufficient drug delivery or is a consequence of drug-drug interactions. One may argue that since we now have a large number of second and third generation AEDs with only a mild tendency to or no drug interactions, the issue of drug-drug interactions has become outdated.[9] A number of circumstances, however, make this less likely. First, it is unclear to what extent the classic AEDs are being prescribed in daily neuro-oncological practice as compared to second or third generation AEDs. Studies on physician compliance show that EIAEDs are routinely given to patients with brain tumors as seizure prophylaxis, despite current guidelines advising against this practice.[108–110] In a recent survey of 28 Australian cancer centers, the enzyme-inducer phenytoin was given as first-line anticonvulsant, followed by levetiracetam and carbamazepine.[111] Still, in many underdeveloped nations the first generation anticonvulsants are the preferred choice, and we have no good insight to what extent in the developed world financial hurdles restrain the prescribing of newer AEDs. Even if one prescribes an AED that does not kindle drug-drug interactions, it is important to realize that many recently approved AEDs are themselves susceptible to the inducing or inhibiting effects of concurrent chemotherapeutic drugs or tyrosine kinase inhibitors, implying risks of insufficient seizure control or central nervous system toxicity.[68,112] In addition, some of the most recently approved AEDs are not exempt from drug interactions, particularly eslicarbazepine and perampanel.[11]

For clinical practice, it is important to realize that in case of coenzyme-dependent conversion of a parent drug into its active metabolite, a concurrently given enzyme inducer not only causes accelerated metabolism of the parent drug, but also enhanced formation of the active metabolite. In this way, the net effect will be enhanced drug activity. Examples are combined use of an EIAED with cyclophosphamide, ifosfamide, or thiotepa, and a number of tyrosine kinase inhibitors, including erlotinib, imatinib, gefitinib, lapatinib, and sorafenib.[113]

As many tyrosine kinase inhibitors are 3A4 inhibitors, particularly crizotinib and imatinib, one may expect toxicity when combined with 3A4-substrate drugs including some AEDs and chemotherapeutic agents. Although trials of new tyrosine kinase inhibitors in gliomas often include an analysis of the pharmacokinetic effects of concurrent AED use, little is known about how tyrosine kinase inhibitors may affect the metabolism of AEDs. The size of these interactions may well be comparable to the effects on other 3A4 substrate drugs.[68] As tyrosine kinase inhibitors often cause autoinhibition of their own metabolism, the effects of enzyme inhibition on concurrent therapy are often limited. A big obstacle for obtaining factual data on the influence of tyrosine kinase inhibitors on a concurrent therapy is that once an agent has been approved and introduced to the market, it is difficult to find the means for additional drug trials. An exception might be studies on new drug indications for other cancer types than those already approved. It would be a great advantage if such additional investigations include pharmacokinetics on common drug associations in systemic cancer and neuro-oncology, particularly how tyrosine kinase inhibitors affect the metabolism of concurrent therapies such as AEDs and glucocorticoids.

A separate problem is the large variability among individuals with respect to the metabolism of drugs. The activity of CYP enzymes shows high individual variability, including their susceptibility to the effects of drug inducers or inhibitors. The efficacy of PXR and GC receptor as transcription factors involved in regulating these enzymes is also variable, contributing to differences in enzyme activity among individuals.[5,103] CYP activity is also dependent on age, sex, and ethnicity, as well as dietary and organ factors like hepatic dysfunction.[12,114]

The observations on variability in drug metabolism underscore the need of therapeutic drug monitoring by measuring drug concentrations in plasma to detect drug-drug interactions.[11,12,94,95,114] In this way, underdosing or overdosing of AEDs can be recognized, allowing drug adjustment in case of insufficient effectiveness or toxicity.[10,115] To what extent therapeutic drug monitoring is applied in daily neuro-oncologypractice is uncertain and harmful interactions may take place at a larger scale than we assume.[4]

Unfortunately, there are few studies on the value of drug monitoring for the proper management of epilepsy, although low therapeutic AED levels carry a higher risk of seizures.[116] A recent guideline of the American Academy of Neurology and International League of Epilepsy (ILEA) on combined AED and retroviral therapy is fully based on therapeutic-drug-monitoring data.[117] A position paper of the ILAE has defined when to apply therapeutic drug monitoring in the daily practice of seizure management.[115] The ILAE recommends performing plasma drug measurements once a desired clinical response has been achieved based on the variable therapeutic range of an AED, the persistence of seizures, and factors as age, comorbidity or concomitant therapy. Similar calls for therapeutic drug monitoring of chemotherapeutics and tyrosine kinase inhibitors have been made in the field of systemic cancer treatment.[86,94,95,115,118] Given the prevalence of multidrug regimens for patients with seizures and cancer, routine monitoring of plasma levels of AEDs and anticancer agents is probably indispensable.

Electronic databases can be consulted to provide easy access and information on drug interactions with AEDs.[119–121] However, these may contain large discrepancies, particularly for newer generation AEDs.[122] In this review, these shortcomings have been avoided by reporting on all studies examining interactions between AEDs and chemotherapeutic drugs, tyrosine kinase inhibitors, or glucocorticoids and expressing these in quantitative rather than qualitative terms.

In conclusion, the risks of drug-drug interactions causing ineffective cancer treatment, organ dysfunction, or neurotoxicity illustrate the importance of effective and well-tolerated AEDs that do not interfere with cancer treatment. The strongest effects of the EIAEDs carbamazepine, phenytoin, and phenobarbital are seen with cyclophosphamide, camptothecin derivatives, taxanes, and topoisomerase II inhibitors, showing about a 2-fold to 3-fold higher clearance and a doubling of maximum tolerated dose. The inhibiting activity of valproic acid is mainly limited to temsirolimus, and it may aggravate thrombopenia caused by chemotherapeutic drugs via a direct effect on the bone marrow. Cisplatin and high-dose methotrexate lead to lower plasma levels of phenytoin, valproic acid, tiagabine, and clobazam or other benzodiazepines by competition for protein binding. The enzyme-inhibiting effect of 5-fluorouracil causes a 2-fold to 4-fold higher organ exposure to phenytoin and phenobarbital. Many tyrosine kinase inhibitors are 3A4 inhibitors, particularly imatinib and crizotinib, requiring lower dosing of concurrent therapy.

As more than 50% of patients with gliomas need AED polytherapy, the risk of drug-drug interaction is not easily avoidable. If possible, the EIAEDs carbamazepine, phenytoin, and phenobarbital should be avoided. Fortunately, there are a number of effective and well-tolerated AEDs that cause little to no drug interactions; these include levetiracetam, lamotrigine, lacosamide, and zonisamide.[9] Although many of the tyrosine kinase inhibitors are 3A4 inhibitors, it not known how strongly they affect concurrent therapy. The routine of treating of low-grade and high-grade gliomas or brain metastasis with multidrug regimens consisting of AEDs, chemotherapeutics, tyrosine kinase inhibitors, and glucocorticoids, combined with the individual variability in drug metabolism, underlines the importance of plasma drug monitoring. Similar calls for therapeutic drug monitoring of chemotherapeutic drugs and tyrosine kinase inhibitors have been made for systemic cancer. Future studies on the pharmacokinetics of AEDs with concurrent antitumor agents, particularly tyrosine kinase inhibitors and glucocorticoids, will hopefully provide more insight into the size of these interactions, allowing the proper dosing of combined therapies.

Websites to be consulted on Drug Interactions:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm
http://www.micromedexsolutions.com/home/dispatch
https://www.clinicalpharmacology.com
http://www.uptodate.com/crlsql/interact/frameset.jsp.

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