

Research Paper

The Impact of Concomitant Medication Use on Patient Eligibility for Phase I Cancer Clinical Trials

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Abstract

Concomitant medication (CM) use may result in Phase I cancer clinical trial ineligibility due to concern for potential CM-investigational drug interactions or alteration of investigational drug absorption. Few studies have examined the impact of CM use on trial eligibility. **Methods:** We reviewed records of 274 patients on Phase I trials at a single academic institution. Demographics, CM identities and classes, CM discontinuation, reasons, and incidence of CM substitution were recorded. CM-investigational drug cytochrome P450 (CYP) enzyme interactions were documented. Statistical analysis was performed using descriptive statistics. **Results:** 273 of 274 patients (99.6%, 95% confidence interval [CI] 98.9-100%) took CM, with a median of 8 CM per patient (range 0 – 42). CM discontinuation occurred in 67 cases (25%, 95% CI 19-30%). The most common CM classes discontinued were herbal (17 cases, 25%, 95% CI 16-37%) and proton pump inhibitors (15 cases, 22%, 95% CI 12-32%). CM discontinuation reasons were: protocol prohibition (32 cases, 48%, 95% CI 36-60%); potential CM-investigational drug interaction (25 cases, 37%, 95% CI 26-49%); other (10 cases, 15%, 95% CI 6-23%). A potential CM-investigational drug CYP interaction was noted in 122 cases (45%, 95% CI 39-50%). CM potentially weakly decreased investigational drug metabolism in 52 cases (43%, 95% CI 34-51%), and potentially strongly decreased investigational drug metabolism in 17 cases (14%, 95% CI 8-20%). Investigational drug potentially weakly decreased CM metabolism in 39 cases (32%, 95% CI 24-40%), and potentially strongly decreased CM metabolism in 28 cases (23%, 95% CI 15-30%). CM substitution occurred in 36/67 cases (54%, 95% CI 41-66%) where CM were discontinued to allow for eventual participation in clinical trials. Overall in 2 cases (0.7%, 95% CI 0.1-2.6%), patients were protocol ineligible because CM could not be discontinued or substituted. **Conclusions:** This study highlights the high prevalence of concomitant medication use among cancer patients enrolled in phase I clinical trials. Most patients did meet trial eligibility criteria with careful substitution and discontinuation of CM. The most common reason for discontinuation of CM was protocol prohibition. The most common medications discontinued were herbal, proton pump inhibitors, selective serotonin reuptake inhibitor anti-depressants, and non-steroidal anti-inflammatory drugs.

Key words: Concomitant, Medications, Cancer, Clinical Trials, Eligibility, Drug Interactions.

INTRODUCTION

Clinical trials are essential to new drug development and approval. Phase I trials of investigational agents for cancer are a key step in cancer drug development. The primary objective of a Phase I trial is to determine the maximum tolerated dose (MTD), administration schedule and toxicity profile of an investigational drug. In oncology, Phase I trials provide a suitable option for patients who have exhausted available lines of therapy, or for those patients for whom no standard therapy exists. (1)

Fewer than 5% of cancer patients enroll in cancer clinical trials. (2) Factors related to this low rate of participation include physicians who are unaware of suitable cancer clinical trials for patients, poor patient performance status, patient preferences, and stringent inclusion and exclusion criteria of study protocols. Although appropriate eligibility criteria are essential to conduct a scientifically rigorous study, unduly restrictive inclusion and exclusion criteria diminish generalization of study results to real-world clinical practice and potentially limit patient participation.

Medication-related exclusion criteria are among the most common barriers to enrollment in clinical trials. A systematic review of randomized controlled trials identified 54.1% of trials to have at least one medication-related exclusion criterion. (3) Almost all patients have other co-morbidities and cancer-related symptoms that require administration of concomitant medications. As such, cancer clinical trials with rigorous medication-related exclusion criteria potentially could exclude a large number of cancer patients. Careful consideration and justification of all exclusion criteria, especially medication-related exclusion criteria, thus are important to the design of cancer clinical trials.

Limited data are available in the medical literature about concomitant medication use among patients enrolled in cancer clinical trials. Even less information has been published about management of potential concomitant medication/investigational drug interactions. A prior study evaluated the relationships between the number and types of concomitant medications administered to patients on the first day of phase 1 clinical trials and demographics, outcome measures and toxicities. (4) Although the number CM correlated directly with poor performance status there was no association with toxicities or response to therapy and CM. However, more information with regards to types of CM, reasons for discontinuation, feasibility of medication substitution, most common medications discontinued and the number of patients prohibited from study secondary

to CM use was lacking.

To better understand concomitant medication use by patients enrolling in cancer clinical trials, we conducted a retrospective review of patients referred for cancer trials at a dedicated cancer clinical trials center. We sought to determine the most frequently discontinued classes of drugs and the most common reasons why these drug classes must be discontinued. We also examined which drugs can be substituted acceptably in situations where concomitant medications must be discontinued due to interaction with investigational drugs. Finally, we evaluated the proportion of patients excluded from cancer clinical trials due to concomitant medication use.

METHODS

To improve understanding of concomitant medication use among patients enrolling in cancer clinical trials, a retrospective review was performed. We examined the records of 274 consecutive patients referred to Translational Genomics Clinical Research Services (TCRS), located at the Virginia G. Piper Cancer Center in Scottsdale, Arizona, evaluated for Phase I cancer clinical trials between January 1, 2006 and December 31, 2008. During this period, 42 Phase I clinical trials were conducted.

Prior to enrolling subjects on a clinical trial at TCRS, all study subjects' medications were reviewed by an investigational drug pharmacist for potential interactions with investigational drugs. Potential cytochrome P450 enzyme interactions between concomitant medications and investigational agents were documented using University of Indiana's reference tools of drug interactions that are the result of competition for or effects on human cytochrome P450 system. (5) CM potential impact on the absorption of investigational drug as well as CM prohibited by the study protocol were recorded. In cases where concomitant medications had to be discontinued, the pharmacist prepared a list of drugs that could substitute the medication acceptably. A clinician confirmed the investigational drug interaction report.

From 274 consecutive investigational drug interaction reports, data were collected, including basic patient demographics (age, sex, tumor type), concomitant drug names and classes, identities of concomitant drugs that were discontinued and the reasons for discontinuation, and incidence of drug substitutions. We defined a medication as "herbal" if it was a botanical substance, animal-derived extract, vitamin, mineral, fatty acid, protein, probiotic, or "functional food," according to the National Center for Complementary and Alternative Medicine definition of "biologically based practices." (6). Cytochrome

P450 (CYP) enzyme interactions between concomitant medication and the investigational agent were documented. We categorized these interactions as weak, moderate, or strong inhibition or induction of an investigational drug's or a concomitant drug's metabolism via a cytochrome P450 isoenzyme. Statistical analysis was performed using descriptive statistics including medians and ranges, as well as proportions with 95% confidence intervals (CIs) based on a normal approximation.

RESULTS

Patient demographics are presented in Table 1. The median age was 62 years (range 24 - 90 years) with a balanced gender distribution. All patients were being treated for cancer in the metastatic or refractory setting, had failed prior standard therapies, and/or had no standard therapy available. A wide variety of cancer types were seen.

Table 1. Demographic data of patients referred for Phase I cancer clinical trials.

CHARACTERISTIC	NO. OF PATIENTS	% OF PATIENTS
Age (years)		
Mean (SD)	60.3 (13.8)	-
Median (range)	62 (24-90)	
Sex		
Male	146	53
Female	128	47
Tumor Type		
Pancreatic	52	20
Colorectal	29	11
Prostate	24	9
Breast	19	7
Non-Small Cell Lung	16	6
GIST	13	5
Non-Melanoma Skin	13	5
Ovarian	10	4
Melanoma	9	3
Cervical	8	3
Other†	81	30

SD, standard deviation; GIST, gastrointestinal stromal tumor

† Adenocarcinoma unknown primary (n = 1); adrenocortical (n = 5); acute lymphoblastic leukemia (n = 2); acute myeloid leukemia (n = 6); anal (n = 2); angiosarcoma (n = 1); bladder (n = 4); carcinoid (n = 2); carcinoma of unknown primary (n = 1); endometrial (n = 1); esophageal (n = 3); Ewing's sarcoma (n = 1); gastric (n = 7); gastroesophageal (n = 1); head/neck (n = 4); hepatocellular (n = 3); Hodgkin lymphoma (n = 1); leiomyosarcoma (n = 2); liposarcoma (n = 3); lung, not otherwise specified (n = 4); mesothelioma (n = 2); neuroendocrine (n = 3); primary peritoneal (n = 1); pheochromocytoma (n = 1); renal cell (n = 2); salivary gland (n = 3); sarcoma, not otherwise specified (n = 5); small cell lung (n = 3); small intestine (n = 1); thyroid (n = 1); vaginal (n = 2).

The vast majority of patients were taking concomitant medications (273 of 274 patients; 99.6%, 95% CI 98.9-100%). The median number of concomitant medications per patient was 8 (range 0 - 42). The frequencies of the most commonly used drugs and drug classes are shown in Table 2. The most commonly used agent was over-the-counter multivitamins, taken by 108(39%, 95% CI 34-45%) of patients. The most common non-herbal medications used were lorazepam, hydrocodone/APAP, and prochlorperazine.

The overall rate of CM discontinuation occurred in 67 (25%, 95% CI 19-30%) of the 273 patients on concomitant medications. The 67 patients had 1 or more concomitant medication discontinued. A large proportion of these 67 patients (48 patients, 72%, 95% CI 61-82%) had just 1 concomitant medication discontinued (range 1 - 23 concomitant medications discontinued). The most common class of concomitant medication discontinued was herbal (17 cases, 25%, 95% CI 16-37%). The most common prescription medication discontinued include proton pump inhibitors (15 cases, 22%, 95% CI 12-32%), selective serotonin reuptake inhibitors (9 cases, 13%, 95% CI 10-29%) and non-steroidal anti-inflammatory drugs (6 cases, 9%, 95% CI 2-16%).

Concomitant medications were discontinued most often because they were specifically prohibited by the study protocol (32 cases, 48%, 95% CI 36-60%). One or more study protocols prohibited concomitant use of the drug classes listed in Table 3. Concomitant use of various drug classes were most often prohibited due to potential CYP interactions with the investigational medication. The only drug classes which were discontinued but not prohibited by any study protocol were dopamine reuptake inhibitor anti-depressants, opioids and sleep insomnia agents. These medications, when discontinued, were discontinued for reasons of increased risk of seizures and potential CYP interaction without study protocol directed prohibition. When concomitant medications were discontinued for reasons other than study protocol prohibition, the most common reason was a potential CYP interaction with the investigational drug that was identified by the reviewing investigational pharmacist. Pharmacist-recommended concomitant medication discontinuation due to CYP interactions occurred in 25 cases (37%, 95% CI 26-49%) of the 67 cases in which CM discontinuation occurred.

A majority of patients took one or more herbal medications (143/274 patients, 52%, 95% CI 46-58%). Aside from multivitamins, oral or intravenous ascorbic acid (42 patients), B-vitamins (41 patients), fish oil (24 patients), flaxseed oil (17 patients), coenzyme Q-10

(13 patients), glucosamine/chondroitin (12 patients) and "Acidophilus" (10 patients), were among the most commonly used products. A total of 42 herbal medications were discontinued among 23 patients, as shown in Table 4. The most common reason for their discontinuation was a potential CYP interaction with the investigational drug that was identified by the reviewing pharmacist.

In total, a potential concomitant medication-investigational drug CYP interaction was noted in 122 cases (45%, 95% CI 39-50%). Concomitant medications potentially weakly decreased investigational drug metabolism in 52 cases (43%, 95% CI 34-51%), and potentially strongly decreased investigational drug metabolism in 17 cases (14%, 95% CI 8-20%). Investigational drugs potentially weakly decreased concomitant medication metabolism in 39

cases (32%, 95% CI 24-40%), and potentially strongly decreased concomitant medication metabolism in 28 cases (23%, 95% CI 15-30%).

When concomitant medications had to be discontinued, it was possible to substitute other acceptable medications in 36/67 cases (54%, 95% CI 41-66%). A list of drugs that were discontinued, and drugs that were acceptably substituted for them, is presented in Table 5. Drugs discontinued generally were substituted with another drug from the same class that had less potential for CYP interactions with the investigational drug. Two patients were prohibited from clinical trial enrollment due to concomitant medication use (one patient due to use of famotidine; one patient due to use of warfarin). These medications could not be discontinued or substituted in either case.

Table 2. Most common used concomitant medications among patients referred for Phase I cancer clinical trials.

DRUG	NO. OF PATIENTS USING DRUG	%* OF PATIENTS USING DRUG (95% CI)	NO. OF CASES DRUG DISCONTINUED (%**, 95% CI)
Herbals			
Multivitamins	108	40 (34-46)	0
Sennosides	55	20 (16-25)	0
Other misc. herbal supplements	47	17 (13-22)	16 (24, 14-36)
Oral ascorbic acid	39	14 (10-19)	1 (1, 0-8)
Fish oil	24	9 (6-13)	0
B-Vitamin	23	8 (5-12)	0
Vitamin D	23	8 (5-12)	0
Non-herbal Prescription			
Lorazepam	50	18 (14-23)	0
Hydrocodone/APAP	48	18 (13-23)	0
Prochlorperazine	48	18 (13-23)	0
Oxycodone/APAP	40	15 (11-19)	0
Warfarin	38	14 (10-19)	4 (6, 2-15)
Oxycodone	37	14 (10-18)	1 (1, 0-8)
Pantoprazole	32	12 (8-16)	1 (1, 0-8)
Potassium	29	11 (7-15)	0
Levothyroxine	25	9 (6-13)	0
Diphenoxylate/Atropine	24	9 (6-13)	0
Oxycontin	24	9 (6-13)	0
Zolpidem	24	9 (6-13)	0
Morphine sulfate controlled release	23	8 (5-12)	0
Zoledronic acid	21	8 (5-12)	0
Hydromorphone	20	7 (5-11)	0
Lisinopril	20	7 (5-11)	0
Omeprazole	20	7 (5-11)	4 (6, 2-15)
Non-herbal OTC			
Calcium carbonate	42	15 (11-20)	0
Acetaminophen	39	14 (10-19)	0
Ibuprofen	37	14 (10-18)	5 (7, 2-17)
Aspirin	30	11 (8-15)	0
Diphenhydramine	23	8 (5-12)	1 (1, 0-8)

APAP, acetaminophen. OTC, over-the-counter. CI, confidence interval.

* Out of 273 patients using concomitant medications.

** Out of 67 patients who discontinued concomitant medications.

Table 3. Classes of drugs discontinued and reasons for drug discontinuation among patients referred for Phase I cancer clinical trials.

DRUG CLASS DISCONTINUED	DRUG	NO. OF CASES DISCONTINUED	REASONS DISCONTINUED (NO. OF CASES)
Angiotensin converting enzyme inhibitor	Enalapril	1	D
Anti-androgen agent	Bicalutamide	1	D
Antibacterial	Nitrofurantoin	1	D
	Sulfamethoxazole/Trimethoprim	2	C, D
Anticoagulant	Warfarin	4	C (1) D (3)
Antifungal	Fluconazole	1	C, D
	Voriconazole	1	C
Antihistamine	Diphenhydramine	1	D
	Loratidine	1	C
Anti-lipidemic agent	Atorvastatin	1	C
	Ezetimibe	1	C, D
	Simvastatin	1	C
Anti-neoplastic tyrosine kinase inhibitor	Imatinib	1	D
Aromatase inhibitor	Anastrozole	1	D
Calcium channel blocker	Amlodipine	2	C
	Diltiazem	1	D
Decongestant	Oxymetolazone	1	D
Diuretic	Furosemide	1	C, D
Dopamine reuptake inhibitor anti-depressant	Bupropion	1	E
Gonadotropin releasing hormone	Leuprolide	1	C, D
H2 Receptor antagonist (anti-acid)	Cimetidine	1	C, D
	Famotidine	1	D
Non-steroidal anti-inflammatory	Ibuprofen	5	C (3) D (1) C+D (1)
	Naproxen	1	D
Oral chemotherapeutic agent	Mitotane	1	D
Opioid	Oxycodone	1	C
Phenothiazine anti-emetic	Prochlorperazine	1	D
Proton pump inhibitor	Lansoprazole	4	D
	Omeprazole	4	C (1) D (3)
	Pantoprazole	5	C (2) D(3)
	Rabeprazole	2	D
Selective serotonin reuptake inhibitor anti-depressant	Citalopram	1	D
	Escitalopram	1	A
	Paroxetine	2	C, D
	Sertraline	5	B (1) C (3) C+D (1)
Sleep insomnia agent	Zolpidem	1	B
Steroid	Prednisone	3	B (1) D (2)

Reasons for drug discontinuation: A - patient preference; B unspecified; C - potential cytochrome P450 enzyme interaction; D - prohibited by study protocol; E - increased risk of seizure.

Table 4. Herbal supplements discontinued among patients referred for Phase I cancer clinical trials.

HERBAL DRUG CLASS	HERBAL PRODUCT	NO. OF PATIENTS TAKING	NO. DISCONTINUED	REASONS DISCONTINUED
Alkaloids	Montana Yew	1	1	E
Anthocyanosides	Bilberry extract	1	1	C
Anti-cancer herbal supplement	Shark cartilage	1	1	B
Anti-inflammatory, anti-parasite	Ginko biloba	5	2	C
Coagulation agent	Lumbrokinase	1	1	C
Egyptian black cumen	Black seed oil	1	1	C
Fruit	Mangosteen	3	1	C
Ginger family	Tumeric	4	2	C
Liquid iodine	Atomidine	1	1	B
Natural angiogenesis inhibitor	Bindweed extract	1	1	B

Phytochemicals	Red Clover, Milk Thistle, Turkish Rhubarb, Blessed Thistle	1	1	F
	Green Tea	3	1	C
	Schizandra	1	1	B
	Bromelain	1	1	C
Proteolytic digestive enzyme	Phytoarteminisin	1	1	B
Sweet wormwood	Ascorbic acid	42	3	C
Other miscellaneous herbal products	"Assimilaid"	1	1	C
	"Alpha 20C"	1	1	C
	Cat's claw	1	1	C
	Chapparal leaf	1	1	D
	"Bio D Mulsion Forte"	1	1	C
	"Cell Forte"	1	1	A
	Chinese mushroom extract	1	1	C
	Cherry Extract	1	1	C
	Echinacea	3	2	C
	Evening primrose	1	1	C
	Flaxseed oil	17	1	C
	"Immunecare"	1	1	B
	Kava kava rhizome	1	1	C
	"Lifeshield Detox"	1	1	C
	"Sportcap"	1	1	C
	Turkey tall mushrooms	1	1	B
	Misc. "mushroom extracts"	1	1	C
	"Power Adapt"	1	1	C
	"Quinary Concentrate"	1	1	B
	"Synergy Plus" w/ ginseng	1	1	C
"XTra Cell Comitris"	1	1	C	

A - patient preference; B - unspecified; C - potential cytochrome P450 enzyme interaction; D - prohibited by study protocol; E - potential chemotherapeutic activity; F - duplicate herbal therapy.

Table 5. Concomitant medications discontinued with corresponding acceptable drug substitutions among patients referred for Phase I cancer clinical trials.

DRUG DISCONTINUED	REASON DISCONTINUED	DRUG SUBSTITUTED
Atorvastatin	B	Pravastatin
Citalopram	C	Escitalopram
Diltiazem	C	Metoprolol
Diphenhydramine	C	Ramelteon
Enalapril	C	Lisinopril
Escitalopram	A	Citalopram
Esomeprazole	B	Famotidine
Furosemide	C	Bumetanide
Ibuprofen	B	Acetaminophen Naproxen
Lansoprazole	C	Calcium carbonate Pantoprazole
Loratidine	B	Fexofenadine
Naproxen	C	Acetaminophen
Omeprazole	B, C	Calcium carbonate Esomeprazole
Oxycodone	B	Morphine sulfate
Nitrofurantoin	C	Ciprofloxacin
Pantoprazole	B, C	Famotidine Ranitidine
Paroxetine	C	Escitalopram
Rabeprazole	C	Ranitidine
Sertraline	B, C	Citalopram Escitalopram
Simvastatin	B	Ezetemibe Pravastatin
Prochlorperazine	C	Ondansetron
Venlafaxine	C	Bupropion
Voriconazole	B	Posaconazole
Warfarin	C	Enoxaparin

A - patient preference; B - potential cytochrome P450 enzyme interaction; C - prohibited by study protocol.

DISCUSSION

Concomitant medication use by patients enrolling in Phase I cancer clinical trials is nearly universal, yet little attention is given to this topic in the medical literature. Most reports of Phase I trials do not contain a description of the types of concomitant medications taken by the patients on the trial, or how those medications might interact with the drug under study. (4) This report of patients referred for Phase I cancer clinical trials greatly augments the limited body of knowledge in this area by establishing the frequency of concomitant medication use, the rate of and reasons for concomitant medication discontinuation, the most common medications discontinued, the feasibility of medication substitution and the number of patients that were excluded from clinical trials due to concomitant medication use.

We found a very high rate of concomitant medication use among patients referred for Phase I cancer clinical trials (99.6%). Most patients took a high number of concomitant medications (median of 8 drugs per patient, with a range of 0 to 42 concomitant medications per patient). A similar rate of concomitant medication use (90.9% of patients) was found in a review of 690 patients enrolled on Phase I trials of anti-cancer agents at a large academic practice. (4) The study evaluated relationship between the number and type of concomitant medication administration on the first day of phase I clinical trial and demographic characteristics, outcomes and toxicities. On this study, we choose to further delineate the prevalence of concomitant medication use and discontinuation rate in patients in phase I clinical trial. We also wanted to evaluate the most common class of medications discontinued, reasons for discontinuation and feasibility of substitution with similar class-medication. Based on our results, concomitant medication use appears to be higher in the cancer patient population than the amount of use associated with other diseases. For example, a report of subjects enrolled in a trial of ziprasidone, an antipsychotic agent for treatment of schizophrenia, found 78% of patients taking concomitant medications. (7) In a study of the pharmacokinetics of escitalopram, a drug used for treatment of major depression, 76% of patients were taking additional medications. (8) A study of levetiracetam, an anticonvulsant agent, reported 83% of study patients taking at least 1 concomitant medication. (9) Other studies of concomitant medication use in epilepsy and Alzheimer's disease have reported rates of concomitant medication use to be in the 70-75% range, (10-12) although one study of donepezil in Alzheimer's disease found 93% of patient taking at least 1 concomi-

tant medication. (13)

Cancer patients are more likely to take more concomitant medications than patients with other illnesses for two reasons: to minimize disease-related symptoms and, as in the case of herbal medication use, electively. Patients with cancer have many symptoms and conditions caused by the cancer, including, but not limited to, pain, nausea, constipation, anorexia, cough, dyspnea, neuropathy, depression and anxiety. To mitigate these comorbidities, physicians utilize concomitant medications. Thus, a patient with just 1 or 2 of the previously mentioned problems might be given several different medications to address each problem, such as a stool softener plus a stimulant laxative for constipation, as well as an opioid plus an anti-epileptic drug for neuropathy. Indeed, over one-half of patients in this review were taking an opioid for pain. Moreover, concomitant medications may be substituted as the co-morbidity they treat may have less morbidity potential compared to underlying the malignancy. Additionally, many cancer patients choose to take over-the-counter drug supplements, or "herbal" medications, under the belief that these substances have anti-cancer properties. Over half of the patients studied self-administered "herbal" product, and 39% were taking multivitamins.

Despite the high amount of concomitant medication use, the proportion of medications discontinued in an individual patient was low. When necessary, only 1 medication had to be eliminated in the majority of cases. "Herbal" products, proton pump inhibitors, selective serotonin reuptake inhibitors and non-steroidal anti-inflammatory drugs were the most common drug classes that were discontinued. A potential cytochrome P450 enzyme interaction was the most common reason for "herbal" products to be discontinued, whereas prohibition by study protocol appeared to be a more common reason for discontinuation of the other drug classes.

In situations where concomitant medications were discontinued and substituted, another drug from the same class with less potential for CYP interaction with the investigational drug was often substituted. Furthermore, in most cases when a drug was discontinued, substitution was not required. According to our findings in cases where concomitant medications were discontinued substitution was successful in 54% of the cases, while in the remaining cases substitution was not necessary. The findings clearly suggest that acceptable solutions may be found for most patients taking concomitant medications either prohibited by a study protocol or having potential interactions with a investigational drug. It should, there-

fore, be uncommon for a patient to be excluded from a cancer clinical trial due to concomitant medication use, as our findings confirm.

Although the majority of patients in this review were able to eventually enroll in cancer clinical trials, this was possibly achieved largely through judicious evaluation and intervention by an investigational pharmacy team. Sites that do not have such availability could potentially be unable to successfully enroll similar patients. As noted, a systematic review of randomized controlled trials identified 54.1% of trials to have at least one medication-related exclusion criterion. In 36.6% of the trials, the medication-related exclusion criterion was "poorly justified." Drug intervention trials and industry-sponsored trials were significantly more likely to have a medication-related exclusion criterion. (3) We also identified other studies of treatments for non-cancer related conditions that did not allow concomitant medication use. (14-16) Although such exclusion criteria allow researchers to identify statistically significant associations between drug administration and outcomes by minimizing confounders (by limiting use of concomitant medications that might affect investigational drug absorption or metabolism), these criteria lessen external validity and applicability to everyday clinical practice.

Furthermore, a previous report of concomitant medication use among patients enrolled on Phase I cancer clinical trials showed that concomitant medication use does not impact the dose of investigational drug recommended for Phase II testing. Toxicities and response to investigational therapy in these trials also were not impacted by concomitant medication use. (4) This finding is particularly important, since toxicity assessments help to determine the MTD of an investigational drug in a Phase I trial.

Several additional trials have shown no impact on concomitant medication use and outcome. For example, a study of infliximab pharmacokinetics showed that use of concomitant medications including prednisolone, omeprazole, non-steroidal anti-inflammatory drugs and analgesics did not affect infliximab pharmacokinetics. (17) Other studies have shown no impact on escitalopram serum levels with concomitant medication use (8); no effect on donepezil tolerability despite concomitant medication use (11); no increase in gastrointestinal side effects with concomitant use of donepezil and non-steroidal anti-inflammatory drugs (13); no increase in bradycardia risk with concomitant use of donepezil and beta-blockers, calcium channel blockers or digoxin (13); and no association between concomitant medication use and adverse events or discontinuation of

sertraline because of adverse events, even for patients taking 5 or more concomitant medications. (19)

Given the first-in-man nature of most of the cancer clinical trials conducted at TCRS, in which the objective is to determine a MTD, it could be argued that prohibiting any concomitant medication that might alter investigational drug absorption or metabolism is justified to allow as accurate a MTD determination to be made as possible. However, prohibiting certain drugs or drug classes should not translate to complete ineligibility for a Phase I cancer clinical trial if a patient happens to be taking a prohibited drug. Rather, every effort should be made to find a drug with less potential interaction with the investigational drug to allow patient participation. Taken together, the findings of this study and those findings from previous reports in which concomitant medication use had little bearing on outcomes, (4, 8, 11, 13, 17-19) we conclude that acceptable drug substitutions or discontinuations could be made in nearly every case to allow patient enrollment in cancer clinical trials, without impacting trial results.

The study's limitations include its retrospective nature, which might bias results due to a non-random selection of patients. Additionally, we did not correlate response to therapy and use of concomitant medications for these patients, so no conclusions about concomitant medications and their impact on treatment response can be made. Finally, concomitant medication use and impact on investigational drug pharmacokinetics was not evaluated as part of this study. These could be addressed by future trials with analysis of inter-subject variability of investigational drug pharmacokinetics in relation to concomitant medication use.

It is estimated that over 750 new medications are in development for cancer treatment. (20) Since most, if not all, cancer patients have symptoms from the underlying disease that must be controlled with concomitant medications, it is likely that pharmacokinetic and safety evaluations of all new cancer therapies in development will be conducted in the presence of concomitant medications. Therefore, efforts to substitute or discontinue concomitant medications, when appropriate, will allow conduct of Phase I trial results in a generally encountered population of cancer patients with advanced disease and associated co-morbidities. Additionally, this study highlights the importance of an investigational pharmacist review of patient medications for potential investigational drug and concomitant medication interactions. Such input from pharmacy colleagues enables the clinician-investigator to both conduct a scientifically rigorous clinical trial and adequately address the needs

of the study patient.

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All authors have contributed significantly to the study and preparation of the manuscript, and have approved the final version.

CONFLICT OF INTEREST

There are no financial disclosures from any of the authors.

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