

Oral Anticancer Drugs: How Limited Dosing Options and Dose Reductions May Affect Outcomes in Comparative Trials and Efficacy in Patients

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ABSTRACT

Historically, cancer medicine has avoided the problem of unequal dosing by comparing maximum-tolerated doses of intravenous regimens with proportionate dose reductions for toxicity. However, in recent years, with the development of numerous oral anticancer agents, dosing options are arbitrarily and increasingly limited by the size of pills. We contend that an underappreciated consequence of pill size is unequal dosing in comparative clinical trials and that this can have an impact on outcomes. We discuss how comparative effectiveness trials can be unbalanced and how the use of doses that are not sustainable might affect outcomes, especially marginal ones. We further argue that because of their poor tolerability and their limited dosing options, which often result in large dose adjustments in response to toxicity, the real-world clinical effectiveness of oral anticancer agents may be diminished and may not emulate results achieved in registration trials.

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INTRODUCTION

The development of orally administered, targeted small molecules was grounded in the concept of “cancer as a chronic disease,” and it was hoped that they would be an improvement on intravenous agents. Aimed at genes important to cancer cells but less relevant to normal tissues, targeted therapies were expected to have few adverse effects, an attractive property for drugs envisioned to be administered daily. Unfortunately, the last decade has taught us that adverse effects of targeted therapies have not been fewer than those with cytotoxic agents, as evidenced by inordinately high rates of dose reductions and drug discontinuation.^{1,2}

Here, we address the issue of oral anticancer drug dosing. After citing evidence that drug levels, adverse effects, and efficacy are correlated, we consider the impact that unequal dosing may have in comparative clinical trials. The proliferation of targeted therapies, many with similar properties and competing indications, has resulted in comparative clinical data, often with small yet statistically significant differences. In accordance with principles of fair comparative effectiveness research, comparison between active agents should use comparable doses.³ But in some trials, this has not been the case. We conclude by expressing

concern that restricted dosing and frequent dose reductions may reduce the effectiveness of oral anticancer agents in the community.

DRUG LEVELS, ADVERSE EFFECTS, AND EFFICACY: THE IMPORTANCE OF DRUG DOSING

Evidence exists that correlates drug levels and adverse effects with the efficacy of oral targeted anticancer therapies as summarized in Table 1.⁴⁻¹³ Thus, it is not surprising that ingested drug doses are important. Phase I studies frequently provide evidence that ingested doses and serum concentrations have an impact on drug efficacy,⁴⁻¹⁴ and these observations are bolstered by data from late-phase studies. One such late-phase study is a retrospective analysis of phase III data with sunitinib in advanced or metastatic renal cell carcinoma (mRCC) that found a clear relationship between administered dose and tumor shrinkage. The authors concluded that their analysis “highlights the importance of maintaining patients on a 50-mg dose of sunitinib and striving to avoid unscheduled dosing interruptions or titration during treatment.”⁴ As a second example, a phase IV study of sorafenib in Japan found that relative dose intensity could predict progression-free survival (PFS) among patients with cytokine-treated mRCC.¹⁵

Table 1. Drug Levels, Adverse Effects, and Efficacy

Reference	Drug	Disease	No. of Patients	Observation	Correlation	
					Outcome	PCC
					HR	P
Association of Drug Levels and Efficacy						
Houk et al ⁴	Sunitinib	mRCC	146	↑ AUC _{ss} of sunitinib + SU12662*	↑ TTP	.001
					↑ OS	.010
			149	↑ AUC _{ss} of sunitinib + SU12662*	↑ ORR	< .001
			149	↑ AUC _{ss} of sunitinib + SU12662*	↑ SD	.002
			278	↑ AUC _{ss} of sunitinib + SU12662*	↑ TTP	.001
					↑ OS	.001
			225	↑ AUC _{ss} of sunitinib + SU12662*	↑ SD	< .001
Rini et al ⁵	Axitinib	mRCC	49	Cycle 1/day 1, 2 hours post-dose drug concentrations, 45.2-56.4 ng/mL	↑ ORR	
			49	Cycle 1/day 1, 2 hours post-dose drug concentrations, 45.2-56.4 ng/mL	↑ Median PFS and OS	
Rini et al ⁶	Axitinib	mRCC	168	AUC ≥ 300 h·ng/mL†	↑ Median PFS and OS	.001
			168	Every 100 h·ng/mL ↑ in AUC†	↑ PFS	.001
			168	Every 100 h·ng/mL ↑ in AUC†	↑ OS	.001
					1.5-fold ↑ probability of PR	
Association of Drug Levels and Adverse Effects						
Houk et al ⁴	Sunitinib	Solid tumors, mRCC, GIST	69 of 443	↑ AUC _{ss} of sunitinib	↑ Incidence fatigue, not severity	
				↑ C _{troughTotal} of sunitinib + SU12662*	↑ dBP	0.29
				↑ AUC _{cur28Ttotal} of sunitinib	Greater reductions in ANC	-0.4
Association of Adverse Effects and Efficacy						
Rini et al ⁷	Sunitinib	mRCC	534	Treatment induced hypertension defined by maximum sBP‡	↑ OS, 30.9 v 7.2 months	< .001
					↑ ORR, 54.8% v 8.7%	< .001
					↑ PFS, 12.5 v 2.5 months	< .001
			168	dBP ≥ 90 v < 90 mmHg†	↑ PFS, 14.6 v 7.86 months	< .001
				Every 10 mmHg ↑ of dBP	↑ PFS	.006
				dBP ≥ 90 v < 90 mmHg†	↑ OS, 29.5 v 18.5 months	< .001
				Every 10 mmHg ↑ of dBP	↑ OS	.024
Rini ⁸	Axitinib	Melanoma, mRCC, thyroid cancer, NSCLC	230§	dBP ≥ 90 mmHg 8 weeks after starting axitinib	↑ ORR, 43.9% v 12%	< .001
					↑ PFS, 10.2 v 7.1 months	< .001
					↑ OS, 25.8 v 14.9 months	< .001
Jain ⁹	Sorafenib	CRC	18	HFS grade ≥ 2 v < 2	↑ PFS, 8.7 v 4.7 months	.0065

Abbreviations: ANC, absolute neutrophil count; AUC, area under the concentration-time curve; AUC_{cur28Ttotal}, 28-day cumulative AUC for total drug; AUC_{ss}, steady state AUC; CRC, colorectal cancer; C_{troughTotal}, trough plasma concentration for total drug; dBP, diastolic blood pressure; GIST, GI stromal tumor; HFS, hand-foot syndrome; HR, hazard ratio; mRCC, metastatic renal cell carcinoma; NSCLC, non-small-cell lung cancer; ORR, overall response rate (complete response + partial response [PR]); OS, overall survival; PCC, Pearson correlation coefficient; PFS, progression-free survival; sBP, systolic blood pressure; SD, stable disease; TTP, time to progression.

*Active sunitinib metabolite.
†dBP association more significant than AUC.

‡Similar results when hypertension is defined by maximum dBP with the exception of PFS defined by dBP in a Cox proportional hazard model using hypertension as a time-dependent covariate.

§Pooled analysis includes patients with melanoma, thyroid cancer, NSCLC, and sorafenib-refractory mRCC or cytokine-refractory mRCC.

The extent to which this might be true in malignancies harboring key mutations essential to the phenotype remains unclear. Although one is tempted to think that with key mutations that lead to oncogenic addiction such a correlation might be less, even in these cases, there appears to be some relationship between dose and response. For example, with imatinib, an excellent targeted agent, only two of six patients with chronic myelogenous leukemia receiving a dose of 25 mg per day achieved a partial response, a response rate much lower than that achieved with higher doses.¹⁶ In melanomas harboring *BRAF* mutations, responses to the *BRAF* inhibitor vemurafenib were not observed below a dose of 240 mg orally twice a day.¹⁷

The point is that there is surely a minimum effective dose for all targeted therapies below which measurable efficacy cannot be expected. Agents targeting cellular components such as *BRAF*, *BCR-ABL*, and *EGFR* that are critical to certain cancers may be effective in those cells at doses lower than those established as tolerable, although others such as mammalian target of rapamycin inhibitors¹⁸ may require doses closer to those maximally tolerable. We would also note the underappreciated problem of drug-food interactions: studies have shown that drug levels achieved may vary five- to 10-fold depending on whether the oral dose is taken on an empty or full stomach.^{19,20}

HOW DRUG DOSING MAY AFFECT CLINICAL TRIAL RESULTS

Although dose adjustments and drug discontinuation are not new phenomena, the frequency and magnitude of these occurrences appear to be much higher with oral than with intravenous anticancer agents (Tables 2 and 3). When a large fraction of patients in a trial end up taking doses other than the starting dose, unequal escalations and reductions may assume an important role.

Consider the Axis Trial (Axitinib [AG 013736] As Second Line Therapy For Metastatic Renal Cell Cancer: Axis Trial), a comparative effectiveness study of axitinib and sorafenib in patients with mRCC whose disease had progressed on first-line therapy. We consider the Axis Trial to be an example of an unbalanced trial design.^{22,74} Patients were randomly assigned to either the approved dose of sorafenib (400 mg orally twice a day) or the experimental agent axitinib (5 mg orally twice a day). At first glance, the playing field seems level—a new drug is developed that challenges a commonly used alternative. However, several factors may have resulted in unequal doses being compared. The first was the size of protocol-mandated dose adjustments. Table 4, which shows dose levels in the Axis trial, reveals that at levels other than the starting dose, sorafenib was penalized. For patients experiencing toxicity, doses were reduced. The first step down reduced the sorafenib dose to 50% of the original dose and reduced axitinib to 60% of its starting dose. The second step down reduced sorafenib to 25% of the original dose but axitinib was reduced to only 40% of its starting dose. Importantly, the rules of dose reduction were also uneven. Regarding hypertension, a toxicity seen more frequently with axitinib (40% for all grades) than with sorafenib (29% for all grades), patients assigned to sorafenib had protocol-mandated reductions for hypertension if more than one drug or more intensive therapy than was previously required was used to control blood pressure (ie, grade 3 toxicity according to Common Terminology Criteria for Adverse Events [CTCAE], version 3.0).⁹⁴ In the axitinib arm, doses were reduced only when patients achieved either a systolic pressure above 150 mmHg or a diastolic pressure above 100 mmHg on two separate

readings and only after their antihypertensive treatment had been optimized. Thus, dose reductions for sorafenib were mandated at a lower threshold than those for axitinib, and therefore, it is not surprising that 54% of patients (192 of 355) taking sorafenib had dose reductions, but only 34% of patients (121 of 359) taking axitinib had dose reductions. Furthermore, patients taking axitinib whose blood pressure did not exceed 150/90 mmHg were permitted an initial dose escalation to a 40% higher dose, and if this was tolerated, a second escalation to a 100% higher dose was permitted; in 132 patients (37%), the axitinib dose was increased to more than 5 mg twice a day. However, sorafenib dose escalations were not allowed. All of these design features introduced the potential for unidirectional bias. Although one may argue that axitinib was better tolerated than sorafenib and less likely to undergo a dose reduction, this does not satisfy concerns regarding the magnitudes of and the different standards for dose reduction. It also does not satisfy concerns regarding differences in the ability to escalate doses. Some might argue that sorafenib doses were similar to those used in earlier trials^{32,37} and similar to those advised by the US Food and Drug Administration (FDA) label, but smaller dose reductions could have been planned. In addition, dose escalations also created an imbalance, with axitinib allowed to have 40% to 100% dose increases. Although we recognize that the sorafenib dose usually has not been increased, a substantial fraction of patients can tolerate doses higher than 400 mg twice a day.⁹⁵ Dose increases in oncology are important because they achieve two outcomes. The first is the administration of higher doses to patients whose tumors appear to be drug sensitive and may be even more responsive to higher doses. The second and most important outcome is administration of an adequate dose to patients who metabolize drug more rapidly. They often tolerate starting doses exceptionally well but might not achieve optimal serum levels. Indeed, updated data from the Axis Trial shows that patients who tolerated dose escalation above the starting dose required these higher doses to achieve outcomes comparable to those of patients who could not have their dose escalated, suggesting that patients who metabolized drug rapidly needed higher doses.⁹⁶ Thus, although patients receiving axitinib who may have metabolized drug more quickly had an opportunity to achieve an optimal oral dose, the same cannot be said for those randomly assigned to sorafenib. This is bolstered by a recent randomized phase II study of axitinib among patients with treatment-naïve mRCC that compared a strategy of stable dosing of axitinib at 5 mg twice a day against a titration strategy, allowing dose escalation similar to that in the Axis Trial. The objective response rate among patients in the titration group rose from 34% to 54%.⁹⁷

A second example of trial design that introduced systematic bias is that of tivozanib, another VEGF inhibitor evaluated in mRCC. The TIVO-1 study (A Phase 3, Randomized, Controlled, Multi-Center, Open-Label Study to Compare Tivozanib [AV-951] to Sorafenib in Subjects With Advanced Renal Cell Carcinoma [TIVO-1]) randomly assigned patients with mRCC to either tivozanib at a starting dose of 1.5 mg a day or sorafenib 400 mg twice a day.³⁹ Crossover (to tivozanib) was allowed on progression for patients starting on sorafenib but not for those starting with tivozanib. For the first 5 months of the study, PFS favored sorafenib. Then the curves crossed, yielding a median PFSs of 11.9 months for tivozanib and 9.1 months for sorafenib.⁹⁸ What explains this peculiar reversal of fortune? Why would one drug, which takes the early lead, ultimately underperform on the metric of PFS when neither differences in postprotocol therapy

Unequal Dosing in Comparative Trials

Table 2. Dose Reduction and Discontinuation for Oral Targeted Agents

Drug	Dose (mg)	No. of Patients	Disease	% of Patients With Dose Reduction	% of Patients Who Discontinued Treatment	Reference
Sorafenib	400	299	NSCLC	N/R	17.7	Wakelee et al ²¹
Sorafenib	400	355	RCC	52.1	9.3	Rini et al ²²
Sorafenib	400	229	HCC	72.5	40.6	Kudo et al ²³
Sorafenib	400	129	RCC	34.9	22.5	Naito et al ²⁴
Sorafenib	400	62	RCC	30.6	6.5	Procopio et al ²⁵
Sorafenib	400	71	OC/PPC	N/R	12.7	Matei et al ²⁶
Sorafenib	400	82	SCLC	N/R	23.2	Gitlitz et al ²⁷
Sorafenib	400	55	UC	40	3.6	Nimeiri et al ²⁸
Sorafenib	400	64	PC	N/R	6.3	Safarinejad ²⁹
Sorafenib	400	51	NSCLC	27.5	11.8	Blumenschein et al ³⁰
Sorafenib	400	52	RCC	28.8	N/R	Di Lorenzo et al ³¹
Sorafenib	400	452	RCC	13	10	Escudier et al ³²
Sorafenib	400	97	RCC	33	11.4	Escudier et al ³³
Sorafenib	400	51	HCC	33.3	N/R	Yau et al ³⁴
Sorafenib	400	150	HCC	30.7	14.7	Cheng et al ³⁵
Sorafenib	400	56	WDTC	52	33.9	Kloos et al ³⁶
Sorafenib	400	297	HCC	26	38	Llovet et al ³⁷
Sorafenib	400	55	PC	N/R	N/R	Steinbild et al ³⁸
Sorafenib	400	137	HCC	N/R	19.7	Abou-Alfa et al ³⁹
Sorafenib	400	202	RCC	N/R	4.4	Ratain et al ⁴⁰
Median, sorafenib				33	12.7	
Mean, sorafenib				36.5	16.8	
Sunitinib	50	51	Pleural mesothelioma	41.2	9.8	Nowak et al ⁴¹
Sunitinib	50	146	RCC	36.3	15.8	Motzer et al ⁴²
Sunitinib	37.5	143	RCC	42.7	17.5	
Sunitinib	37.5	56	Biliary CA	21.4	17.9	Yi et al ⁴³
Sunitinib	37.5	119	RCC	32.8	10.1	Barrios et al ⁴⁴
Sunitinib	50	84	NSCLC	17.9	19	Gervais et al ⁴⁵
Sunitinib	37.5	64	NSCLC	26.6	12.5	Novello et al ⁴⁶
Sunitinib	50	52	Gastric CA	9.6	3.8	Moehler et al ⁴⁷
Sunitinib	37.5	83	PNET	31.3	18.1	Raymond et al ⁴⁸
Sunitinib	50	74	PACA	28.4	9.4	O'Reilly et al ⁴⁹
Sunitinib	50	51	RCC	78.4	25.4	Tomita et al ⁵⁰
Sunitinib	50	78	Gastric CA	18	30.8	Bang et al ⁵¹
Sunitinib	37.5	238	Breast CA	28.2	15.1	Barrios et al ⁵²
Sunitinib	37.5	107	RCC	43	15	Escudier et al ⁵³
Sunitinib	50	375	RCC	50	19	Motzer et al ⁵⁴
Sunitinib	37.5	60	GIST	23.3	6.7	George et al ⁵⁵
Sunitinib	50	61	RCC	N/R	11.5	Rini et al ⁵⁶
Sunitinib	50	107	NET	47.7	10.3	Kulke et al ⁵⁷
Sunitinib	50	64	Breast CA	39.1	N/R	Burstein et al ⁵⁸
Sunitinib	50	63	NSCLC	22.2	49.2	Socinski et al ⁵⁹
Sunitinib	50	84	CRC	31	8.3	Saltz et al ⁶⁰
Sunitinib	50	105	RCC	N/R	11.4	Motzer et al ⁶¹
Sunitinib	50	63	RCC	35	3.17	Motzer et al ⁶²
Median, sunitinib				31.3	13.8	
Mean, sunitinib				33.5	15.4	
Pazopanib	800	290	RCC	N/R	16	Sternberg et al ⁶³
Pazopanib	800	240	STS	38.3	15.4	van der Graaf et al ⁶⁴
Pazopanib	800	74	Cervical CA	N/R	17.6	Monk et al ⁶⁵
Pazopanib	800	225	RCC	31.1	15.1	Hutson et al ⁶⁶
Pazopanib	800	142	STS	23.2	6.3	Slejfer et al ⁶⁷
Vandetanib	300	617	NSCLC	N/R	12.1	Lee et al ⁶⁸
Vandetanib	300	72	WDTC	22.2	33.3	Leboulleux et al ⁶⁹
Vandetanib	300	231	MTC	35.1	12.1	Wells et al ²
Vandetanib	300	623	NSCLC	N/R	14.4	Natale et al ⁷⁰
Vandetanib	300	83	NSCLC	N/R	26.5	Natale et al ⁷¹
Vandetanib	300	73	NSCLC	N/R	N/R	Heymach et al ⁷²
Vandetanib	300	52	SCLC	N/R	N/R	Arnold et al ⁷³
Axitinib	5	359	RCC	34	7.5	Motzer et al ⁷⁴

(continued on following page)

Table 2. Dose Reduction and Discontinuation for Oral Targeted Agents (continued)

Drug	Dose (mg)	No. of Patients	Disease	% of Patients With Dose Reduction	% of Patients Who Discontinued Treatment	Reference
Axitinib	5	64	RCC	65.6	20.3	Tomita et al ⁷⁵
Axitinib	5	62	RCC	45.2	35.5	Rini et al ⁷⁶
Axitinib	5	60	Thyroid CA	38.3	13.3	Cohen et al ⁷⁷
Axitinib	5	52	RCC	28.8	19.2	Rixe et al ⁷⁸
Regorafenib	160	133	GIST	N/R	7.5	Demetri et al ⁷⁹
Regorafenib	160	500	CRC	37.6	17	Grothey et al ⁸⁰
Cabozantinib	100	171	PC	62	24	Smith et al ¹
Cabozantinib	140	220	MTC	79	27	Schoffski et al ⁸¹
Tivozanib	1.5	260	RCC	9	8	Nosov et al ⁸²
Cediranib	45	53	RCC	N/R	11.3	Mulders et al ⁸³
Median, all				33.2	14.9	
Mean, all				36	16.4	

NOTE. Values were obtained from publications listed, clinicaltrials.gov, information contained in package inserts, meeting abstract presentations, and US Food and Drug Administration announcements.

Abbreviations: CA, cancer; CRC, colorectal carcinoma; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; MTC, medullary thyroid cancer; NET, neuroendocrine tumor; N/R, not reported; NSCLC, non-small cell lung cancer; OC, ovarian cancer; PACA, pancreatic adenocarcinoma; PC, prostate carcinoma; PNET, pancreatic neuroendocrine tumor; PPC, primary peritoneal cancer; RCC, renal cell carcinoma; SCLC, small cell lung cancer; STS, soft tissue sarcoma; UC, uterine carcinoma/carcinosarcoma; WDTC, well-differentiated thyroid cancer.

nor crossover could have an impact? Unequal dose reductions might explain the paradoxical findings. The first dose reduction with tivozanib was from the starting dose of 1.5 mg to a dose of 1.0 mg, a reduction to 66% of the starting dose. Sorafenib was reduced from 400 mg twice a day to 400 mg once a day, a reduction to 50% of the starting dose and an adjustment downward of 50% greater than the adjustment for tivozanib. Rates of dose reduction were unequal, with 14% of patients receiving tivozanib and 43% of patients receiving sorafenib requiring dose reductions.⁹⁸ Thus, many patients receiving sorafenib took a big step down, while fewer patients receiving tivozanib took a smaller step. Different rules for dose reduction in the setting of hypertension may have played a role; the TIVO-1 study, like the Axis Trial,

permitted more antihypertensive therapy for tivozanib than for sorafenib before the dose was reduced. Finally, we note that the reversal in PFS occurs at approximately the same time that an effect resulting from the dose reductions might have begun.

A third example of potential bias occurred in the RECORD-3 study (Efficacy and Safety Comparison of RAD001 Versus Sunitinib in the First-line and Second-line Treatment of Patients With Metastatic Renal Cell Carcinoma [RECORD-3]) that randomly assigned untreated patients with mRCC to either 10 mg of everolimus or 50 mg of sunitinib with crossover to the other drug on progression.⁹⁹ The trial ultimately found superiority in both PFS (10.7 to 7.9 months) and overall survival (32.0 to 22.4 months) for patients who received

Table 3. Dose Reduction and Discontinuation for Intravenous Agents

Drug	Dose (mg/m ²)	Schedule (day)	No. of Patients	Disease	% of Patients With Dose Reduction	% of Patients Who Discontinued Treatment	Reference
Pemetrexed	500	1	1,725	NSCLC	1.5	1.2	Scagliotti et al ⁸⁴
Cabazitaxel	25	1	755	Prostate	12	5	de Bono et al ⁸⁵
Nab-paclitaxel	100	1, 8, 15	1,052	NSCLC	46	4	Socinski et al ⁸⁶
Eribulin	1.4	1, 8	762	Breast	29	10.2	Cortes et al ⁸⁷
Nab-paclitaxel	100	1, 8, 15	300	Breast	N/R	8	Gradishar et al ⁸⁸
FOLFOX-4 or XELOX without bevacizumab			701	Colorectal	N/R	20	Saltz et al ⁸⁹
Paclitaxel	80	1, 7, 14	1,231	Breast	29	12	Sparano et al ⁹⁰
Paclitaxel	175	1	1,253	Breast	22	5	Sparano et al ⁹⁰
Gemcitabine (plus vinorelbine)	1,200 (30)	1, 8	125	Breast	N/R	3	Martin et al ⁹¹
Vinorelbine	30	1, 8	127	Breast	N/R	5	Martin et al ⁹¹
Gemcitabine	1,000	Once per week × 7 weeks; then days 1, 8, 15	284	Pancreatic	5	6	Moore et al ⁹²
Docetaxel	75	1	335	Prostate	8-12*	11	Tannock et al ⁹³
Docetaxel	30	1, 8, 15, 22, 29	334	Prostate	8-12*	16	Tannock et al ⁹³
Mitoxantrone	12	1	337	Prostate	8-12*	10	Tannock et al ⁹³
Median, all					8-12	7	
Mean, all					17.5	8.3	

Abbreviations: FOLFOX-4, infusional fluorouracil, leucovorin, and oxaliplatin, with fluorouracil infused over 22 hours on days 1 and 2; N/R, not reported; NSCLC, non-small-cell lung cancer; XELOX, capecitabine plus oxaliplatin.

*Value of 10 was used in calculations of mean.

Table 4. Starting Doses and Prespecified Dose Adjustments in the Axis Trial

Drug	Second Dose Reduction			First Dose Reduction			Starting Dose		First Dose Escalation			Second Dose Escalation		
	Dose (mg)	Schedule	% Starting Dose	Dose (mg)	Schedule	% Starting Dose	Dose (mg)	Schedule	Dose (mg)	Schedule	% Starting Dose	Dose (mg)	Schedule	% Starting Dose
Axitinib	2	Twice a day	40	3	Twice a day	60	5	Twice a day	7	Twice a day	140	10	Twice a day	200
Sorafenib	400	Once every other day	25	400	Once a day	50	400	Twice a day	None allowed			None allowed		

sunitinib as initial treatment. RECORD-3 may have inadvertently penalized the sponsor’s agent, everolimus, through unequal dose reductions. The dose of everolimus was initially reduced to 5 mg a day and then to 5 mg every other day (50% and 25% of the starting dose, respectively), while sunitinib was reduced first to 37.5 mg and then to 25 mg a day (75% and 50% of the starting dose, respectively; S. Gogov, personal communication, October 2013). Because doses of both agents are frequently reduced and because everolimus was penalized at all doses in addition to the starting dose, at least some portion of the difference in outcomes may be explained by imbalances in dosing.

By using a multifaceted strategy for searching MEDLINE and Google Scholar databases, we identified eight head-to-head trials of oral anticancer agents with reported outcomes, including five in solid tumors that used unequal dose adjustment schemes, four of which concluded that the penalized drug was inferior.^{22,98-104} In addition, we identified two studies that were actively recruiting or were as yet unpublished in which unequal dose reduction schemes were confirmed with the sponsor: the first was an ongoing trial (A Study of Cabozantinib [XL184] vs Everolimus in Subjects With Metastatic Renal Cell Carcinoma [METEOR]) comparing cabozantinib with everolimus in mRCC (ie, cabozantinib 60 mg→40 mg→20 mg and everolimus 10 mg→5 mg→2.5 mg; Exelixis corporate representative, personal communication, December 2013). The second was a trial (Cabozantinib-s-malate or Sunitinib Malate in Treating Patients With Previously Untreated Locally Advanced or Metastatic Kidney Cancer) that likely uses unequal dosing in comparing cabozantinib with sunitinib in mRCC (cabozantinib, 60 mg→40 mg→20 mg and sunitinib 50 mg→37.5 mg→25 mg).

DOSE REDUCTIONS AND EFFICACY IN PATIENTS

Unfortunately, in the era of targeted therapies, concerns regarding dose reductions apply to many patients. For many oral agents, the percentage of patients undergoing dose reductions is substantial and could be clinically important. Discontinuation, often in the setting of grade 1 or 2 toxicities, has underscored the importance of the duration of toxicities. Low-grade toxicities occurring daily may be less tolerable than higher-grade toxicities that resolve rapidly.¹⁰⁵ Table 2 summarizes the rates of dose reduction and drug discontinuation of oral agents with putative primary targets of VEGF and RET. This collection, encompassing 66 clinical trials that enrolled 50 or more patients, shows that about one third of patients had their administered doses reduced. Compare this with much lower rates of dose reduction and discontinuation with contemporaneously developed intravenous agents shown in Table 3. With oral targeted therapies, dose reductions are occurring frequently, and the magnitudes of those reductions are

often large. Table 5 shows recommended dose reductions from FDA labeling for targeted and cytotoxic therapies developed contemporaneously. The first dose reduction with oral agents is often greater than the dose reduction advised for intravenous agents. As we have already discussed, the available data for oral targeted therapies indicate that the magnitudes of the reductions are such that there is likely to be an impact on effectiveness.

Furthermore, data from real-world clinical practice suggest that reductions may occur at even higher rates when oral agents are administered to a population not as carefully selected as those enrolled onto a trial. It is well known that stringent eligibility criteria in cancer therapy trials can affect the external validity and generalizability of results. Consider an observational study of patients with hepatocellular carcinoma treated with sorafenib at the recommended dose of 400 mg twice a day: 54% required dose reduction and 56% discontinued sorafenib for reasons other than progression.¹⁰⁶ These rates are 50% to 100% higher than the rates of dose reduction and drug discontinuation of 26% and 38% in the original report.³⁷ Also consider data from an expanded-access trial in Italy of sunitinib among patients with mRCC (who were ineligible for other sunitinib studies) in which 46% (238 of 521) required dose reductions.¹⁰⁷ This exceeds the 32% of patients requiring dose reduction in the pivotal study.¹⁰⁸

Finally consider the example of cabozantinib,¹⁰⁹ a tyrosine kinase inhibitor that targets the rearranged during transfection (RET) proto-oncogene, among other kinases, that was approved by the FDA in 2012 for the treatment of medullary thyroid carcinoma. The starting oral dose in the clinical trial and the dose approved by the FDA was 140 mg a day. Twenty-seven percent of patients enrolled onto the registration trial discontinued cabozantinib and, as noted in the FDA approval, “the recommended dose and schedule for cabozantinib is 140 mg orally once daily . . . dose reduction was required in 79% of patients.” Furthermore, the manufacturer recommends dose reductions to 100 and 60 mg (28% and 57% of the starting dose of 140 mg). Can we be confident that these adjustments have no impact on efficacy? Can we be sure private practitioners and patients will persevere through toxicities as much as the clinicians and patients in a clinical trial? If the answers to either of those questions is no, then how can we be sure that outcomes reported in a trial with a dose that only one fifth of patients could tolerate will be emulated in the community? For most, it is not surprising to find that patients with good performance status enrolled onto experimental trials by enthusiastic investigators might tolerate higher doses for a longer period of time, and greater dose reductions by community physicians treating real-world patients have long been a concern.¹¹⁰ We must consider whether dose adjustments are a nearly ubiquitous unappreciated source of diminished effectiveness in the real world. As the authors that examined sunitinib

Table 5. Manufacturer Recommended Dose Reductions From Drug Package Inserts

Drug	Disease	Initial Dose			First Reduction			Second Reduction			Source
		Dose	Schedule	Route of Administration	Dose	Schedule	Route of Administration	Dose	Schedule	Route of Administration	
Sorafenib	RCC, HCC	400 mg	Twice a day	Oral	400 mg	Once a day	Oral	400 mg	Once every other day	Oral	www.accessdata.fda.gov/drugsatfda_docs/label/2011/021923s012lbl.pdf
Sunitinib	GIST, RCC	50 mg	Once a day	Oral	37.5 mg	Once a day	Oral	25 mg	Once a day	Oral	www.accessdata.fda.gov/drugsatfda_docs/label/2012/021938s021s022s023lbl.pdf
Pazopanib	RCC	800 mg	Once a day	Oral	400 mg	Once a day	Oral	200 mg	Once a day	Oral	www.accessdata.fda.gov/drugsatfda_docs/label/2012/021936s021s022s023lbl.pdf
Axitinib	RCC	5 mg	Twice a day	Oral	3 mg	Twice a day	Oral	2 mg	Twice a day	Oral	www.accessdata.fda.gov/drugsatfda_docs/label/2012/202324lbl.pdf
Vandetanib	MTC	300 mg	Once a day	Oral	200 mg	Once a day	Oral	100 mg	Once a day	Oral	www.accessdata.fda.gov/drugsatfda_docs/label/2012/022405s003lbl.pdf
Cabozantinib	MTC	140 mg	Once a day	Oral	100 mg	Once a day	Oral	60 mg	Once a day	Oral	www.accessdata.fda.gov/drugsatfda_docs/label/2012/203756lbl.pdf
Everolimus	RCC, 4 others	10 mg	Once a day	Oral	5 mg	Once a day	Oral	2.5 mg	Once a day	Oral	www.accessdata.fda.gov/drugsatfda_docs/label/2012/022334s018lbl.pdf
Median											-71
Mean											-65
Pemetrexed	NSCLC	500 mg/m ²	Once every 21 days	IV	375 mg/m ²	Once every 21 days	IV	250 mg/m ²	Once every 21 days	IV	www.accessdata.fda.gov/drugsatfda_docs/label/2013/021462s042lbl.pdf
Cabazitaxel	Prostate CA	25 mg/m ²	Once every 21 days	IV	20 mg/m ²	Once every 21 days	IV	N/R	N/R	—	www.accessdata.fda.gov/drugsatfda_docs/applletter/2013/201023Orig1s007ltr.pdf
Nab-paclitaxel	NSCLC	100 mg/m ²	Days 1, 8, 15; every 21 days	IV	75 mg/m ²	Days 1, 8, 15; every 21 days	IV	50 mg/m ²	Days 1, 8, 15; every 21 days	IV	www.accessdata.fda.gov/drugsatfda_docs/label/2012/021660s031lbl.pdf
Nab-paclitaxel	MBC	260 mg/m ²	Once every 21 days	IV	220 mg/m ²	Once every 21 days	IV	180 mg/m ²	Once every 21 days	IV	-30
Eribulin	Breast CA	1.4 mg/m ²	Days 1, 8; every 21 days	IV	1.1 mg/m ²	Days 1, 8; every 21 days	IV	0.7 mg/m ²	Days 1, 8; every 21 days	IV	www.accessdata.fda.gov/drugsatfda_docs/label/2012/201532s004lbl.pdf
Median											-50
Mean											-45

Abbreviations: CA, cancer; GIST, GI stromal tumor; HCC, hepatocellular carcinoma; IV, intravenous; MBC, metastatic breast cancer; MTC, medullary thyroid cancer; N/R, not reported; NSCLC, non-small-cell lung cancer; RCC, renal cell carcinoma.

cautioned: “in those patients for whom it may not be possible to maintain a full dose, use of alternative dosing schedules. . . may provide benefit in some patients; however, this supposition requires verification in further analysis of additional data.”⁷⁴ Unfortunately, incentives to follow that advice are limited.

OBJECTIONS

There are objections and limitations to this analysis. One may contend that some instances of unequal dosing occur when sponsors adhere to the dose reduction schemes advised by the FDA drug label. However, we argue that the FDA label is not absolute, and trialists should base dosing schemes on the totality of available pharmacologic and phase I evidence, with the goal of most accurately and fairly conducting the trial. Alternatively, others may argue that the size of manufactured pills or capsules contributes to these problems and, to a certain degree, it does. In contrast to intravenous medications, in which any dose can be formulated by the pharmacy, pills and capsules can be dosed only in increments of their smallest size, or half that, for those that can be split. While acknowledging that this is a choice made by manufacturers, it can lead to bias in studies if not handled properly, and it places limits on future trialists. We argue that in a comparative trial, dose levels can and should be made more equitable. For instance, a recent study of sorafenib in well-differentiated thyroid cancer, which achieved its efficacy end point, used a smaller first dose reduction to 75% of the starting dose.¹¹¹

Some limitations to our analysis must be acknowledged. The inability to access dosing information for all published and ongoing studies precludes a comprehensive appraisal of the extent of the concerns noted here. In addition, our analysis compared dose reduction primarily on the basis of percentage changes. However, it is possible that, for certain comparisons, percentages fail to capture biologic equivalence. For example, a 50% reduction of one drug may be equivalent to a 30% reduction of another. We are not aware of evidence to firmly support or refute these claims for any particular comparison; however, this is an assumption and should be acknowledged as such.

In summary, we have outlined what we perceive as an underappreciated but pressing problem in oncology—the dosing of oral anti-

cancer medications and its effect in clinical trials and, more importantly, in the practice of oncology. We have outlined why a comparative effectiveness trial may not be balanced. Readers and editors should query whether dose reductions were of similar sizes, occurred frequently or infrequently, and were made on the basis of comparable rules. If the answers to any of these questions is no, caution is warranted in the interpretation of trial results. In general, we favor smaller step sizes that would allow for a range of titrated doses.

The issue of dosing is important in the conduct of comparative clinical trials since hardwired bias incorporated into a trial cannot be corrected after the fact. Rather, it can only be recognized. But these issues may be even more important in the everyday management of patients. The question one must ask is, Why should a patient with a terminal disease receive a drug at a dose that has never been proven effective and that in the context of accumulated knowledge is likely ineffective? Why should patients receive a 50% dose of a drug they cannot tolerate at full dose rather than seek an alternate treatment? How many oncologists would treat a curable intermediate-grade lymphoma with 50% doses of R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone)? The answer is obviously none. Knowing that full doses of most oral targeted agents are only marginally effective in most patients, and with the evidence suggesting that 50% doses are ineffective for the majority of such compounds, one can argue that this is an issue not only of efficacy but also of optimal patient care.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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Collection and assembly of data: All authors

Data analysis and interpretation: All authors

Manuscript writing: All authors

Final approval of manuscript: All authors

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