Title

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

Journal

Journal of Clinical Oncology, 32(15)

ISSN

0732-183X

Authors

Prasad, Vinay
Massey, Paul R
Fojo, Tito

Publication Date

2014-05-20

DOI

10.1200/jco.2013.53.0204

Peer reviewed

VOLUME 32 · NUMBER 15 · MAY 20 2014

JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

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

Vinay Prasad, Paul R. Massey, and Tito Fojo

See accompanying editorial on page 1537

Vinay Prasad and Tito Fojo, National Cancer Institute, National Institutes of Health, Bethesda, MD; and Paul R. Massey, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA.

Published online ahead of print at www.jco.org on April 7, 2014.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Vinay Prasad, MD, Medical Oncology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bldg 10, Rm 12N226, 9000 Rockville Pike, Bethesda, MD 20892; e-mail: vinayak.prasad@nih.gov.

0732-183X/14/3215w-1620w/$20.00

DOI: 10.1200/JCO.2013.53.0204

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.

J Clin Oncol 32:1620-1629. © 2014 by American Society of Clinical Oncology

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	*P*	HR	*P*
Association of Drug Levels and Efficacy									
Houk et al[4]	Sunitinib	mRCC	146	↑ AUC_{ss} of sunitinib + SU12662*	↑ TTP		.001		
					↑ OS		.010		
		mRCC	149	↑ AUC_{ss} of sunitinib + SU12662*	↑ ORR		< .001		
		mRCC	149	↑ AUC_{ss} of sunitinib + SU12662*	↑ SD		.002		
		GIST	278	↑ AUC_{ss} of sunitinib + SU12662*	↑ TTP		.001		
					↑ OS		.001		
		GIST	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				
		mRCC	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				
		mRCC	168	Every 100 h·ng/mL ↑ in AUC†	↑ PFS			0.871	.001
					↑ OS			0.810	.001
		mRCC	168	Every 100 h·ng/mL ↑ in AUC†	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			
				↑ $AUC_{cum28Total}$ 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	0.332	< .001
					↑ ORR, 54.8% *v* 8.7%		< .001		
					↑ PFS, 12.5 *v* 2.5 months		< .001	0.603	< .001
Rini et al[6]	Axitinib	mRCC	168	dBP ≥ 90 *v* < 90 mmHg†	↑ PFS, 14.6 *v* 7.86 months			0.590	.006
				Every 10 mmHg ↑ of dBP	↑ PFS			0.604	< .001
				dBP ≥ 90 *v* < 90 mmHg†	↑ OS, 29.5 *v* 18.5 months			0.622	.024
				Every 10 mmHg ↑ of dBP	↑ OS			0.652	< .001
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	0.76	.107
					↑ OS, 25.8 *v* 14.9 months		< .001	0.55	< .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; $AUC_{cum28Total}$, 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 inhibitors[18] 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-naive 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

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	Sleijfer 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

	Second Dose Reduction			First Dose Reduction			Starting Dose		First Dose Escalation			Second Dose Escalation		
Drug	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

		Initial Dose			First Reduction				Second Reduction					
Drug	Disease	Dose	Schedule	Route of Administration	Dose	Schedule	Route of Administration	%	Dose	Schedule	Route of Administration	%	Label Date	Source
Sorafenib	RCC, HCC	400 mg	Twice a day	Oral	400 mg	Once a day	Oral	−50	400 mg	Once every other day	Oral	−75	10/14/11	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	25 mg	Once a day	Oral	−50	11/16/12	www.accessdata.fda.gov/drugsatfda_docs/label/2012/021938s021s022s023lbl.pdf
Pazopanib	RCC	800 mg	Once a day	Oral	400 mg	Once a day	Oral	−50	200 mg	Once a day	Oral	−75	11/15/12	www.accessdata.fda.gov/drugsatfda_docs/label/2012/021938s021s022s023lbl.pdf
Axitinib	RCC	5 mg	Twice a day	Oral	3 mg	Twice a day	Oral	−40	2 mg	Twice a day	Oral	−60	1/27/12	www.accessdata.fda.gov/drugsatfda_docs/label/2012/202324lbl.pdf
Vandetanib	MTC	300 mg	Once a day	Oral	200 mg	Once a day	Oral	−33	100 mg	Once a day	Oral	−66	10/9/12	www.accessdata.fda.gov/drugsatfda_docs/label/2012/022405s003lbl.pdf
Cabozantinib	MTC	140 mg	Once a day	Oral	100 mg	Once a day	Oral	−29	60 mg	Once a day	Oral	−57	11/29/12	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	−50	2.5 mg	Once a day	Oral	−75	8/29/12	www.accessdata.fda.gov/drugsatfda_docs/label/2012/022334s018lbl.pdf
Median								−40				−71		
Mean								−45				−65		
Pemetrexed	NSCLC	500 mg/m^2	Once every 21 days	IV	375 mg/m^2	Once every 21 days	IV	−25	250 mg/m^2	Once every 21 days	IV	−50	01/18/2013	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	−20	N/R			—	10/4/2012	www.accessdata.fda.gov/drugsatfda_docs/appletter/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	−25	50 mg/m^2	Days 1, 8, 15; every 21 days	IV	−50	10/11/2012	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	−15	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	−21	0.7 mg/m^2	Days 1, 8; every 21 days	IV	−50	02/17/2012	www.accessdata.fda.gov/drugsatfda_docs/label/2012/201532s004lbl.pdf
Median								−21				−50		
Mean								−21				−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."[4] 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 anticancer 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

Conception and design: Vinay Prasad, Tito Fojo
Collection and assembly of data: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Smith DC, Smith MR, Sweeney C, et al: Cabozantinib in patients with advanced prostate cancer: Results of a phase II randomized discontinuation trial. J Clin Oncol 31:412-419, 2013
2. Wells SA Jr, Robinson BG, Gagel RF, et al: Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: A randomized, double-blind phase III trial. J Clin Oncol 30:134-141, 2012
3. Roland M, Torgerson DJ: What are pragmatic trials? BMJ 316:285, 1998
4. Houk BE, Bello CL, Poland B, et al: Relationship between exposure to sunitinib and efficacy and tolerability endpoints in patients with cancer: Results of a pharmacokinetic/pharmacodynamic meta-analysis. Cancer Chemo Pharmacol 66:357-371, 2010
5. Rini BI, de La Motte Rouge T, Harzstark AL, et al: Five-year survival in patients with cytokine-refractory metastatic renal cell carcinoma treated with axitinib. Clin Genitourin Cancer 11:107-114, 2013
6. Rini BI, Garrett M, Poland B, et al: Axitinib in metastatic renal cell carcinoma: Results of a pharmacokinetic and pharmacodynamic analysis. J Clin Pharmacol 53:491-504, 2013
7. Rini BI, Cohen DP, Lu DR, et al: Hypertension as a biomarker of efficacy in patients with metastatic renal cell carcinoma treated with sunitinib. J Natl Cancer Inst 103:763-773, 2011
8. Rini BI, Schiller JH, Fruehauf JP, et al: Diastolic blood pressure as a biomarker of axitinib efficacy in solid tumors. Clin Cancer Res 17:3841-3849, 2011
9. Jain L, Sissung TM, Danesi R, et al: Hypertension and hand-foot skin reactions related to VEGFR2 genotype and improved clinical outcome following bevacizumab and sorafenib. J Exp Clin Cancer Res 29:95, 2010
10. Rugo HS, Herbst RS, Liu G, et al: Phase I trial of the oral antiangiogenesis agent AG-013736 in patients with advanced solid tumors: Pharmacokinetic and clinical results. J Clin Oncol 23:5474-5483, 2005
11. O'Connor OA, Stewart AK, Vallone M, et al: A phase 1 dose escalation study of the safety and pharmacokinetics of the novel proteasome inhibitor carfilzomib (PR-171) in patients with hematologic malignancies. Clin Cancer Res 15:7085-7091, 2009
12. Mross K, Frost A, Steinbild S, et al: A phase I dose-escalation study of regorafenib (BAY 73-4506), an inhibitor of oncogenic, angiogenic, and stromal kinases, in patients with advanced solid tumors. Clin Cancer Res 18:2658-2667, 2012
13. Advani RH, Buggy JJ, Sharman JP, et al: Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. J Clin Oncol 31:88-94, 2013
14. Hurwitz HI, Dowlati A, Saini S, et al: Phase I trial of pazopanib in patients with advanced cancer. Clin Cancer Res 15:4220-4227, 2009
15. Kawashima A, Takayama H, Arai Y, et al: One-month relative dose intensity of not less than 50% predicts favourable progression-free survival in sorafenib therapy for advanced renal cell carcinoma in Japanese patients. Eur J Cancer 47:1521-1526, 2011
16. Druker BJ, Talpaz M, Resta DJ, et al: Efficacy and safety of a specific inhibitor of the BCR-ABL

tyrosine kinase in chronic myeloid leukemia. N Engl J Med 344:1031-1037, 2001

17. Flaherty KT, Puzanov I, Kim KB, et al: Inhibition of mutated, activated BRAF in metastatic melanoma. N Engl J Med 363:809-819, 2010

18. Tanaka C, O'Reilly T, Kovarik JM, et al: Identifying optimal biologic doses of everolimus (RAD001) in patients with cancer based on the modeling of preclinical and clinical pharmacokinetic and pharmacodynamic data. J Clin Oncol 26:1596-1602, 2008

19. Ratain MJ: Flushing oral oncology drugs down the toilet. J Clin Oncol 29:3958-3959, 2011

20. Sharma MR, Karrison TG, Kell B, et al: Evaluation of food effect on pharmacokinetics of vismodegib in advanced solid tumor patients. Clin Cancer Res 19:3059-3067, 2013

21. Wakelee HA, Lee JW, Hanna NH, et al: A double-blind randomized discontinuation phase-II study of sorafenib (BAY 43-9006) in previously treated non-small-cell lung cancer patients: Eastern Cooperative Oncology Group study E2501. J Thorac Oncol 7:1574-1582, 2012

22. Rini BI, Escudier B, Tomczak P, et al: Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): A randomised phase 3 trial. Lancet 378:1931-1939, 2011

23. Kudo M, Imanaka K, Chida N, et al: Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma. Eur J Cancer 47:2117-2127, 2011

24. Naito S, Tsukamoto T, Murai M, et al: Overall survival and good tolerability of long-term use of sorafenib after cytokine treatment: Final results of a phase II trial of sorafenib in Japanese patients with metastatic renal cell carcinoma. BJU Int 108:1813-1819, 2011

25. Procopio G, Verzoni E, Iacovelli R, et al: Sorafenib with interleukin-2 vs sorafenib alone in metastatic renal cell carcinoma: The ROSORC trial. Br J Cancer 104:1256-1261, 2011

26. Matei D, Sill MW, Lankes HA, et al: Activity of sorafenib in recurrent ovarian cancer and primary peritoneal carcinomatosis: A Gynecologic Oncology Group trial. J Clin Oncol 29:69-75, 2011

27. Gitlitz BJ, Moon J, Glisson BS, et al: Sorafenib in platinum-treated patients with extensive stage small cell lung cancer: A Southwest Oncology Group (SWOG 0435) phase II trial. J Thorac Oncol 5:1835-1840, 2010

28. Nimeiri HS, Oza AM, Morgan RJ, et al: A phase II study of sorafenib in advanced uterine carcinoma/carcinosarcoma: A trial of the Chicago, PMH, and California Phase II Consortia. Gynecol Oncol 117:37-40, 2010

29. Safarinejad MR: Safety and efficacy of sorafenib in patients with castrate resistant prostate cancer: A phase II study. Urol Oncol 28:21-27, 2010

30. Blumenschein GR Jr, Gatzemeier U, Fossella F, et al: Phase II, multicenter, uncontrolled trial of single-agent sorafenib in patients with relapsed or refractory, advanced non-small-cell lung cancer. J Clin Oncol 27:4274-4280, 2009

31. Di Lorenzo G, Cartenì G, Autorino R, et al: Phase II study of sorafenib in patients with sunitinib-refractory metastatic renal cell cancer. J Clin Oncol 27:4469-4474, 2009

32. Escudier B, Eisen T, Stadler WM, et al: Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 356:125-134, 2007

33. Escudier B, Szczylik C, Hutson TE, et al: Randomized phase II trial of first-line treatment with sorafenib versus interferon Alfa-2a in patients with metastatic renal cell carcinoma. J Clin Oncol 27:1280-1289, 2009

34. Yau T, Chan P, Ng KK, et al: Phase 2 open-label study of single-agent sorafenib in treating advanced hepatocellular carcinoma in a hepatitis B-endemic Asian population: Presence of lung metastasis predicts poor response. Cancer 115:428-436, 2009

35. Cheng AL, Kang YK, Chen Z, et al: Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: A phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 10:25-34, 2009

36. Kloos RT, Ringel MD, Knopp MV, et al: Phase II trial of sorafenib in metastatic thyroid cancer. J Clin Oncol 27:1675-1684, 2009

37. Llovet JM, Ricci S, Mazzaferro V, et al:. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 359:378-390, 2008

38. Steinbild S, Mross K, Frost A, et al: A clinical phase II study with sorafenib in patients with progressive hormone-refractory prostate cancer: A study of the CESAR Central European Society for Anticancer Drug Research-EWIV. Br J Cancer 97:1480-1485, 2007

39. Abou-Alfa GK, Schwartz L, Ricci S, et al: Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. J Clin Oncol 24:4293-4300, 2006

40. Ratain MJ, Eisen T, Stadler WM, et al: Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. J Clin Oncol 24:2505-2512, 2006

41. Nowak AK, Millward MJ, Creaney J, et al: A phase II study of intermittent sunitinib malate as second-line therapy in progressive malignant pleural mesothelioma. J Thorac Oncol 7:1449-1456, 2012

42. Motzer RJ, Hutson TE, Olsen MR, et al: Randomized phase II trial of sunitinib on an intermittent versus continuous dosing schedule as first-line therapy for advanced renal cell carcinoma. J Clin Oncol 30:1371-1377, 2012

43. Yi JH, Thongprasert S, Lee J, et al: A phase II study of sunitinib as a second-line treatment in advanced biliary tract carcinoma: A multicentre, multinational study. Eur J Cancer 48:196-201, 2012

44. Barrios CH, Hernandez-Barajas D, Brown MP, et al: Phase II trial of continuous once-daily dosing of sunitinib as first-line treatment in patients with metastatic renal cell carcinoma. Cancer 118:1252-1259, 2012

45. Gervais R, Hainsworth JD, Blais N, et al: Phase II study of sunitinib as maintenance therapy in patients with locally advanced or metastatic non-small cell lung cancer. Lung Cancer 74:474-480, 2011

46. Novello S, Camps C, Grossi F, et al: Phase II study of sunitinib in patients with non-small cell lung cancer and irradiated brain metastases. J Thorac Oncol 6:1260-1266, 2011

47. Moehler M, Mueller A, Hartmann JT, et al: An open-label, multicentre biomarker-oriented AIO phase II trial of sunitinib for patients with chemorefractory advanced gastric cancer. Eur J Cancer 47:1511-1520, 2011

48. Raymond E, Dahan L, Raoul JL, et al: Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med 364:501-513, 2011

49. O'Reilly EM, Niedzwiecki D, Hall M, et al: A Cancer and Leukemia Group B phase II study of sunitinib malate in patients with previously treated metastatic pancreatic adenocarcinoma (CALGB 80603). Oncologist 15:1310-1319, 2010

50. Tomita Y, Shinohara N, Yuasa T, et al: Overall survival and updated results from a phase II study of sunitinib in Japanese patients with metastatic renal cell carcinoma. Jpn J Clin Oncol 40:1166-1172, 2010

51. Bang YJ, Kang YK, Kang WK, et al: Phase II study of sunitinib as second-line treatment for advanced gastric cancer. Invest New Drugs 29:1449-1458, 2011

52. Barrios CH, Liu MC, Lee SC, et al: Phase III randomized trial of sunitinib versus capecitabine in patients with previously treated HER2-negative advanced breast cancer. Breast Cancer Res Treat 121:121-131, 2010

53. Escudier B, Roigas J, Gillessen S, et al: Phase II study of sunitinib administered in a continuous once-daily dosing regimen in patients with cytokine-refractory metastatic renal cell carcinoma. J Clin Oncol 27:4068-4075, 2009

54. Motzer RJ, Hutson TE, Tomczak P, et al: Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol 27:3584-3590, 2009

55. George S, Blay JY, Casali PG, et al: Clinical evaluation of continuous daily dosing of sunitinib malate in patients with advanced gastrointestinal stromal tumour after imatinib failure. Eur J Cancer 45:1959-1968, 2009

56. Rini BI, Michaelson MD, Rosenberg JE, et al: Antitumor activity and biomarker analysis of sunitinib in patients with bevacizumab-refractory metastatic renal cell carcinoma. J Clin Oncol 26:3743-3748, 2008

57. Kulke MH, Lenz HJ, Meropol NJ, et al: Activity of sunitinib in patients with advanced neuroendocrine tumors. J Clin Oncol 26:3403-3410, 2008

58. Burstein HJ, Elias AD, Rugo HS, et al: Phase II study of sunitinib malate, an oral multitargeted tyrosine kinase inhibitor, in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol 26:1810-1816, 2008

59. Socinski MA, Novello S, Brahmer JR, et al: Multicenter, phase II trial of sunitinib in previously treated, advanced non-small-cell lung cancer. J Clin Oncol 26:650-656, 2008

60. Saltz LB, Rosen LS, Marshall JL, et al: Phase II trial of sunitinib in patients with metastatic colorectal cancer after failure of standard therapy. J Clin Oncol 25:4793-4799, 2007

61. Motzer RJ, Rini BI, Bukowski RM, et al: Sunitinib in patients with metastatic renal cell carcinoma. JAMA 295:2516-2524, 2006

62. Motzer RJ, Michaelson MD, Redman BG, et al: Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. J Clin Oncol 24:16-24, 2006

63. Sternberg CN, Hawkins RE, Wagstaff J, et al: A randomised, double-blind phase III study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: Final overall survival results and safety update. Eur J Cancer 49:1287-1296, 2013

64. van der Graaf WT, Blay JY, Chawla SP, et al: Pazopanib for metastatic soft-tissue sarcoma (PALETTE): A randomised, double-blind, placebo-controlled phase 3 trial. Lancet 379:1879-1886, 2012

65. Monk BJ, Mas Lopez L, Zarba JJ, et al: Phase II, open-label study of pazopanib or lapatinib monotherapy compared with pazopanib plus lapatinib combination therapy in patients with advanced and recurrent cervical cancer. J Clin Oncol 28:3562-3569, 2010

66. Hutson TE, Davis ID, Machiels JP, et al: Efficacy and safety of pazopanib in patients with

metastatic renal cell carcinoma. J Clin Oncol 28:475-480, 2010

67. Sleijfer S, Ray-Coquard I, Papai Z, et al: Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: A phase II study from the European Organisation for Research and Treatment of Cancer soft tissue and bone sarcoma group (EORTC study 62043). J Clin Oncol 27:3126-3132, 2009

68. Lee JS, Hirsh V, Park K, et al: Vandetanib versus placebo in patients with advanced non–small-cell lung cancer after prior therapy with an epidermal growth factor receptor tyrosine kinase inhibitor: A randomized, double-blind phase III trial (ZEPHYR). J Clin Oncol 30:1114-1121, 2012

69. Leboulleux S, Bastholt L, Krause T, et al: Vandetanib in locally advanced or metastatic differentiated thyroid cancer: A randomised, double-blind, phase 2 trial. Lancet Oncol 13:897-905, 2012

70. Natale RB, Thongprasert S, Greco FA, et al: Phase III trial of vandetanib compared with erlotinib in patients with previously treated advanced non–small-cell lung cancer. J Clin Oncol 29:1059-1066, 2011

71. Natale RB, Bodkin D, Govindan R, et al: Vandetanib versus gefitinib in patients with advanced non–small-cell lung cancer: Results from a two-part, double-blind, randomized phase II study. J Clin Oncol 27:2523-2529, 2009

72. Heymach JV, Paz-Ares L, De Braud F, et al: Randomized phase II study of vandetanib alone or with paclitaxel and carboplatin as first-line treatment for advanced non-small-cell lung cancer. J Clin Oncol 26:5407-5415, 2008

73. Arnold AM, Seymour L, Smylie M, et al: Phase II study of vandetanib or placebo in small-cell lung cancer patients after complete or partial response to induction chemotherapy with or without radiation therapy: National Cancer Institute of Canada Clinical Trials Group Study BR.20. J Clin Oncol 25:4278-4284, 2007

74. Motzer RJ, Escudier B, Tomczak P, et al: Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: Overall survival analysis and updated results from a randomised phase 3 trial. Lancet Oncol 14:552-562, 2013

75. Tomita Y, Uemura H, Fujimoto H, et al: Key predictive factors of axitinib (AG-013736)-induced proteinuria and efficacy: A phase II study in Japanese patients with cytokine-refractory metastatic renal cell carcinoma. Eur J Cancer 47:2592-2602, 2011

76. Rini BI, Wilding G, Hudes G, et al: Phase II study of axitinib in sorafenib-refractory metastatic renal cell carcinoma. J Clin Oncol 27:4462-4468, 2009

77. Cohen EE, Rosen LS, Vokes EE, et al: Axitinib is an active treatment for all histologic subtypes of advanced thyroid cancer: Results from a phase II study. J Clin Oncol 26:4708-4713, 2008

78. Rixe O, Bukowski RM, Michaelson MD, et al: Axitinib treatment in patients with cytokine-refractory metastatic renal-cell cancer: A phase II study. Lancet Oncol 8:975-984, 2007

79. Demetri GD, Reichardt P, Kang YK, et al: Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): An international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 381:295-302, 2013

80. Grothey A, Van Cutsem E, Sobrero A, et al: Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): An international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 381:303-312, 2013

81. Schoffski P, Elisei R, Müller S, et al: An international, double-blind, randomized, placebo-controlled phase III trial (EXAM) of cabozantinib (XL184) in medullary thyroid carcinoma (MTC) patients (pts) with documented RECIST progression at baseline. J Clin Oncol 30:358s, 2012 (suppl; abstr 5508)

82. Nosov DA, Esteves B, Lipatov ON, et al: Antitumor activity and safety of tivozanib (AV-951) in a phase II randomized discontinuation trial in patients with renal cell carcinoma. J Clin Oncol 30:1678-1685, 2012

83. Mulders P, Hawkins R, Nathan P, et al: Cediranib monotherapy in patients with advanced renal cell carcinoma: Results of a randomised phase II study. Eur J Cancer 48:527-537, 2012

84. Scagliotti GV, Parikh P, von Pawel J, et al: Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non–small-cell lung cancer. J Clin Oncol 26:3543-3551, 2008

85. de Bono JS, Oudard S, Ozguroglu M, et al: Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: A randomised open-label trial. Lancet 376:1147-1154, 2010

86. Socinski MA, Bondarenko I, Karaseva NA, et al: Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non–small-cell lung cancer: Final results of a phase III trial. J Clin Oncol 30:2055-2062, 2012

87. Cortes J, O'Shaughnessy J, Loesch D, et al: Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): A phase 3 open-label randomised study. Lancet 377:914-923, 2011

88. Gradishar WJ, Krasnojon D, Cheporov S, et al: Significantly longer progression-free survival with nab-paclitaxel compared with docetaxel as first-line therapy for metastatic breast cancer. J Clin Oncol 27:3611-3619, 2009

89. Saltz LB, Clarke S, Díaz-Rubio E, et al: Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: A randomized phase III study. J Clin Oncol 26:2013-2019, 2008

90. Sparano JA, Wang M, Martino S, et al: Weekly paclitaxel in the adjuvant treatment of breast cancer. N Engl J Med 358:1663-1671, 2008

91. Martín M, Ruiz A, Muñoz M, et al: Gemcitabine plus vinorelbine versus vinorelbine monotherapy in patients with metastatic breast cancer previously treated with anthracyclines and taxanes: Final results of the phase III Spanish Breast Cancer Research Group (GEICAM) trial. Lancet Oncol 8:219-225, 2007

92. Moore MJ, Goldstein D, Hamm J, et al: Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: A phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 25:1960-1966, 2007

93. Tannock IF, de Wit R, Berry WR, et al: Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. New Engl J Med 351:1502-1512, 2004

94. Colevas AD, Setser A: The NCI Common Terminology Criteria for Adverse Events (CTCAE) v 3.0 is the new standard for oncology clinical trials. J Clin Oncol 22:543s, 2004 (suppl; abstr 6098)

95. Amato R, Zhai J, Willis J, et al: A phase II trial of intrapatient dose-escalated sorafenib in patients with metastatic renal cell carcinoma. Clin Genitourin Cancer 10:153-158, 2012

96. Escudier B, Rini BI, Hutson TE, et al: Updated results of the phase 3 AXIS trial: Axitinib vs sorafenib as second-line therapy for metastatic renal cell carcinoma (mRCC). Eur Uro Suppl 11: e81, 2012

97. Rini BI, Melichar B, Ueda T, et al: Axitinib with or without dose titration for first-line metastatic renal-cell carcinoma: A randomised double-blind phase 2 trial. Lancet Oncol 14:1233-1242, 2013

98. Motzer RJ, Nosov D, Eisen T, et al: Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: Results from a phase III trial. J Clin Oncol 31:3791-3799, 2013

99. Motzer RJ, Barrios CH, Kim TM, et al: Record-3: Phase II randomized trial comparing sequential first-line everolimus (EVE) and second-line sunitinib (SUN) versus first-line SUN and second-line EVE in patients with metastatic renal cell carcinoma (mRCC). J Clin Oncol 31: 285s, 2013 (suppl; abstr 4504)

100. Cheng AL, Kang YK, Lin DY, et al: Sunitinib versus sorafenib in advanced hepatocellular cancer: Results of a randomized phase III trial. J Clin Oncol 31:4067-4075, 2013

101. Motzer RJ, Hutson TE, Cella D, et al: Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med 369:722-731, 2013

102. Saglio G, Kim DW, Issaragrisil S, et al: Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med 362:2251-2259, 2010

103. Kantarjian H, Shah NP, Hochhaus A, et al: Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 362:2260-2270, 2010

104. Hutson TE, Lesovoy V, Al-Shukri S, et al: Axitinib versus sorafenib as first-line therapy in patients with metastatic renal-cell carcinoma: A randomised open-label phase 3 trial. Lancet Oncol 14:1287-1294, 2013

105. Edgerly M, Fojo T: Is there room for improvement in adverse event reporting in the era of targeted therapies? J Natl Cancer Inst 100:240-242, 2008

106. Iavarone M, Cabibbo G, Piscaglia F, et al: Field-practice study of sorafenib therapy for hepatocellular carcinoma: A prospective multicenter study in Italy. Hepatology 54:2055-2063, 2011

107. Sternberg C, Bracarda S, Carteni G, et al: Sunitinib expanded-access trial in metastatic renal cell carcinoma (mRCC): Final Italian results. European Cancer Conference 2013, Amsterdam, the Netherlands, September 27-October 1, 2013 (abstr 2707)

108. Motzer RJ, Hutson TE, Tomczak P, et al: Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 356:115-124, 2007

109. Elisei R, Schlumberger MJ, Müller SP, et al: Cabozantinib in progressive medullary thyroid cancer. J Clin Oncol 31:3639-3646, 2013

110. Chang J: Chemotherapy dose reduction and delay in clinical practice: Evaluating the risk to patient outcome in adjuvant chemotherapy for breast cancer. Eur J Cancer 36:S11-S14, 2000

111. Brose MS, Nutting C, Jarzab B, et al: Sorafenib in locally advanced or metastatic patients with radioactive iodine-refractory differentiated thyroid cancer: The phase III DECISION trial. J Clin Oncol 31:6s, 2013 (suppl; abstr 4)

Acknowledgment

We are grateful to Barry Kramer, MD, for his critical reading of the manuscript.