Published OnlineFirst February 15, 2010; DOI: 10.1158/1078-0432.CCR-09-2684

Cancer Therapy: Clinical

Clinical Cancer Research

Phase I Oncology Studies: Evidence That in the Era of Targeted Therapies Patients on Lower Doses Do Not Fare Worse

Rajul K. Jain[1], J. Jack Lee[3], David Hong[1], Maurie Markman[2], Jing Gong[1], Aung Naing[1], Jennifer Wheler[1], and Razelle Kurzrock[1]

Abstract

Purpose: To safely assess new drugs, cancer patients in initial cohorts of phase I oncology studies receive low drug doses. Doses are successively increased until the maximum tolerated dose (MTD) is determined. Because traditional chemotherapy is often more effective near the MTD, ethical concerns have been raised about administration of low drug doses to phase I patients. However, a substantial portion of oncology trials now investigate targeted agents, which may have different dose-response relationships than cytotoxic chemotherapies.

Experimental Design: Twenty-four consecutive trials treating 683 patients between October 1, 2004, and June 30, 2008, at MD Anderson Cancer Center were analyzed. Patients were assigned to a low-dose (≤25% MTD), medium-dose (25-75% MTD), or high-dose (≥75% MTD) group, and groups were compared for response rate, time-to-treatment failure, progression-free survival, overall survival, and toxicity. To remove negatively biasing data from the high-dose group, in a second analysis, patients treated above the MTD were excluded (high-dose group, 75-100% MTD). Of the 683 patients, 97.7% received targeted agents.

Results: Even when excluding patients above the MTD, there was an early trend favoring the low- versus high-dose group in time-to-treatment failure, with 32.9% versus 25.2% of patients on therapy at 3 months ($P = 0.08$). In addition, the low-dose group fared at least as well as the other groups in all other outcomes, including response rate, progression-free survival, overall survival, and toxicity.

Conclusions: These data may help alleviate concerns that patients who receive low drug doses on contemporary phase I oncology trials fare worse and suggest targeted agents may have different dose-response relationships than cytotoxic chemotherapies. *Clin Cancer Res; 16(4); 1289–97. ©2010 AACR.*

Critical to the development of novel anticancer treatments is the study on new drugs and drug combinations in clinical trials (1). The optimal dose of a new drug treatment is usually determined in a phase I clinical trial, and for traditional chemotherapy, the optimal dose has generally been considered to be near the maximum tolerated dose (MTD) of the drug (2). In a phase I trial, the MTD is determined using a dose-escalation scheme, in which consecutively enrolled patient cohorts receive increasing doses of study agent until unmanageable or unsafe side effects emerge (3, 4). The highest tolerated dose defines the MTD. In contrast to phase I studies on other drugs, in which participants are usually healthy volunteers, phase I trials of antineoplastic agents are generally conducted in cancer patients because of the potentially toxic nature of some anticancer drugs. These patients have usually progressed through standard treatments, but they and their physicians often hope that there may be some clinical benefit from participating in a phase I study (5–9). For these reasons, phase I trials carry ethical concerns. Some critics argue that patients in the low-dose cohorts of these dose-seeking studies receive suboptimal or even placebo doses of medication compared with those treated closer to the MTD (3, 10–14). In addition, physicians may be reluctant to refer patients to studies with potentially ineffective dose levels, and patients may be hesitant to participate in phase I trials for the same reason (8, 15).

The paradigm of dosing cancer treatments at or near their MTDs stems from early observations of positively sloped dose-response relationships with classic cytotoxic chemotherapies, which showed increasing efficacy at higher doses (2, 16–19). Many of these early observations were with agents that are indiscriminately cytotoxic such as nucleoside analogues and are not surprising given that, because malignant cells generally divide faster than

Authors' Affiliations: [1]Department of Investigational Cancer Therapeutics (Phase I Program); [2]Department of Gynecological Medical Oncology, Division of Cancer Medicine; and [3]Department of Biostatistics, MD Anderson Cancer Center, Houston, Texas 77030-4009

Corresponding Author: Rajul K. Jain, Division of Cancer Medicine, MD Anderson Cancer Center, Unit 10, 1515 Holcombe Boulevard, Houston, Texas 77030-4009. Phone: 713-792-0057; Fax: 713-792-3708; E-mail: rjain@mdanderson.org.

doi: 10.1158/1078-0432.CCR-09-2684

Published OnlineFirst February 15, 2010; DOI: 10.1158/1078-0432.CCR-09-2684

Translational Relevance

The data presented in this article are immediately and directly translatable to the clinic. These data should alleviate ethical concerns that patients who receive lower drug doses on contemporary phase I oncology trials fare worse than those at higher doses and thereby may impact the decision to use aggressive dose-escalation schemes in phase I studies. In addition, the data suggest targeted agents may have different dose-response relationships than cytotoxic chemotherapies, which may not only affect dose escalation schemes but also guide translational studies of targeted agents.

nonmalignant cells, higher doses induce increased cell-kill through a kinetic mechanism (20). However, many anticancer drugs currently undergoing clinical investigation are not classically cytotoxic but rather are targeted agents that exploit some feature or pathway that is unique to or exaggerated in cancer cells, such as a growth factor receptor, kinase, or angiogenesis pathway. For this reason and because of the ethical issues and patient and physician concerns noted above, we investigated whether patients receiving lower drug doses in contemporary phase I oncology trials are disadvantaged compared with patients receiving higher doses.

Materials and Methods

Trial and participant inclusion and data collection. We evaluated 71 consecutive clinical trials enrolling 1,420 participants between October 1, 2004, and June 30, 2008, in the Phase I Program at MD Anderson Cancer Center for eligibility in this analysis. To be included, a trial had to be a dose-escalation study on systemic therapy that had either reached an MTD or in which at least one patient had received treatment at the maximum planned dose. For all studies, MTD is defined as the dose-level immediately below that dose that produced an unacceptable amount of dose-limiting toxicities, as predefined in each study. The most common precise definition in our studies was the dose level below which at least one third of patients had a dose-limiting toxicity. Twenty-four trials with 683 participants met criteria. Trials that had not yet reached an MTD or maximum planned dose (30 trials; 408 patients), were not dose-escalation studies (10 trials; 196 patients), were local-regional therapies (4 trials; 106 patients), and were not drug trials (3 trials; 27 patients) were excluded. Patients who started a study by May 1, 2008, were included, and response data through June 30, 2008, were used in the analysis. Most trials were multicenter (median, 2; range, 1-5), and MTDs were determined based upon patient responses from all sites. All patients in the analysis were treated at MD Anderson because efficacy data from other trial sites were limited.

This study was conducted in accordance with our Institutional Review Board guidelines. Data were obtained from the electronic patient record system and from standardized clinical trial overview tables used by the department. These tables are maintained on a secure institutional network as an abbreviated database for all trials done in the department.

Treatment dose. Doses administered on each trial were normalized as per the linear relationship dose percentile = [(administered dose - minimum dose) / (maximum dose - minimum dose)] * 100%. For trials that reached an MTD, maximum dose = MTD. For trials in which the maximum planned test dose was tolerated, maximum dose = the maximum planned dose. In this way, values ≤ 100% represent doses at or below the MTD, and values > 100% represent doses above the MTD. For trials with more than one agent, dose percentile is the arithmetic average of the dose percentile calculated for each agent.

Dose percentiles were used to assign patients to arbitrarily defined low (≤25%), medium (>25% to <75%), and high (≥75%) dose groups. In this study, two analyses were done: (*a*) all patients are included (i.e., doses from 0% to >100%) and (*b*) only patients treated at or below the MTD are included (i.e., doses from 0-100%). In the latter, those receiving study drug above the MTD were excluded to reduce negative bias against the high-dose group outcomes due to increased toxicities.

Evaluation of tumor response to treatment. Radiographic treatment responses were reported in each study. Using the WHO (21) criteria and Response Evaluation Criteria in Solid Tumors (22), responses were categorized as complete response, partial response, stable disease, or progressive disease. Complete response is defined as tumor disappearance; partial response, as reduction of at least 50% (WHO) or 30% (Response Evaluation Criteria in Solid Tumors); stable disease, as any response between partial response and progressive disease; and progressive disease, as the appearance of new lesion(s) or increase by at least 25% (WHO) or 20% (Response Evaluation Criteria in Solid Tumors). While imaging study was required for categorization of response as complete response, partial response, or stable disease, progressive disease could additionally be assigned by a phase I physician for significantly worsening tumor-related symptoms (for example, hemoptysis in patient with tumor involving bronchus).

Statistical analysis. To compare differences in baseline patient characteristics among dose groups, one-way ANOVA was applied for age and number of previous treatments; Pearson's χ^2 test, for sex; race, performance status, and tumor type; and Kruskal-Wallis test, for times from cancer diagnosis and end of last treatment to start of phase I treatment.

Percentages of participants with complete response/partial response/stable disease or progressive disease were calculated by simple division, as was the percent of participants that came off study for toxicity (Fig. 1). Estimates of time-to-treatment failure, progression-free survival, and overall survival were calculated by the Kaplan-Meier method (Ref. 23; Figs. 2–4). Time-to-treatment failure

Published OnlineFirst February 15, 2010; DOI: 10.1158/1078-0432.CCR-09-2684

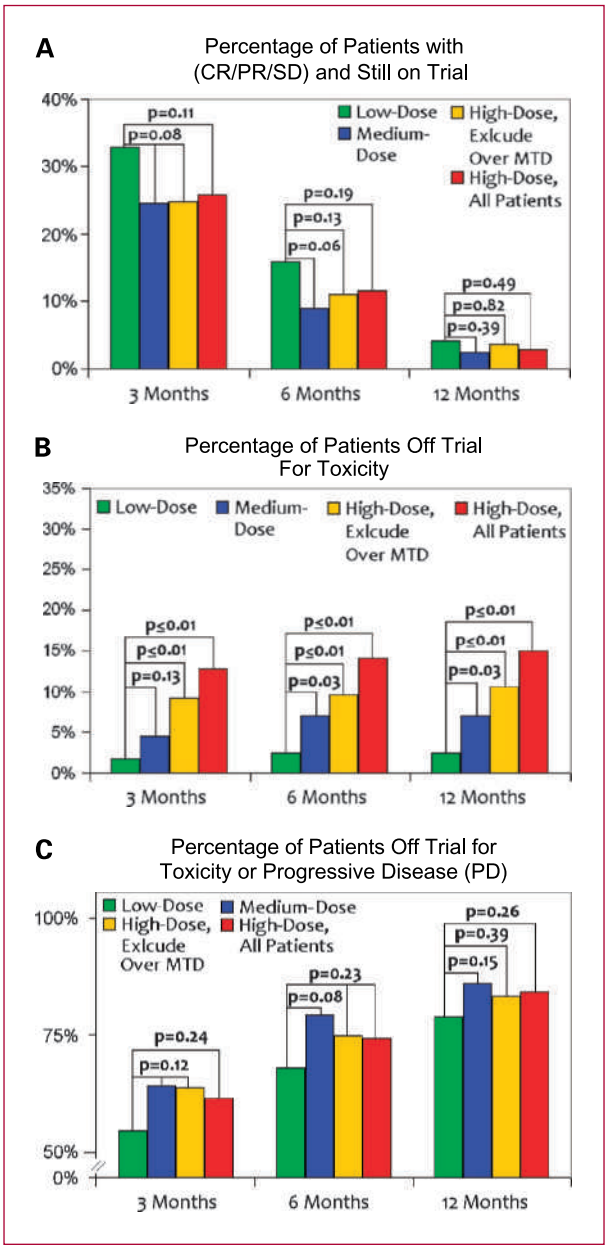

Fig. 1. Response to treatment 3 to 12 mo after starting study. A, percentage of patients with a favorable response that stayed on study. B, percentage off trial due to toxicity. C, percentage off trial due to progressive disease or toxicity.

and progression-free survival differ as follows. In time-to-treatment failure, participants are assigned noncensored end dates when coming off study for any reason and censored end dates only if on study on June 1, 2008. In progression-free survival, participants are assigned noncensored end dates only at the time of progressive disease or death. If a participant started a new treatment before progressive disease or death, the first day of the new treatment is taken as a censored end date given any subsequent effect cannot necessarily be attributed to the original treatment. As with time-to-treatment failure, when calculating progression-free survival and overall survival, patients are assigned censored end dates if still on study on June 1, 2008. Given these differences, progression-free survival primarily captures the tumor response to therapy, whereas time-to-treatment failure captures the tumor response in addition to other reasons a treatment may fail, for example, because of toxicities.

P values are calculated from the corresponding tests including the Cox proportional hazards model, and two-sided *P* values ≤ 0.05 are taken to be significant. All statistical analyses were done using R version 2.8.0 (R Foundation for Statistical Computing).

Results

Trial and participant characteristics. We analyzed 24 phase I studies, including 683 participants, with a median of 22 participants per trial (range, 11-68; Table 1). Most of the trials were of single agents (18 trials), whereas five combined two agents and one combined three agents. The median number of dose levels evaluated was five (range, 3-13). The trials tested agents that span a broad range of antitumor mechanisms (Table 1), and at least one targeted or biological agent was part of the study regimen for 97.7% of participants.

Baseline participant characteristics were equally distributed among the low- (n = 170), medium- (n = 200), and high- (n = 218 or 313 for excluding and not excluding patients treated over the MTD, respectively) dose groups, with no statistically significant difference in any variable (Table 2). The mean age for all participants was 55.7 years, 55.2% were male, and 77.9% were White. Approximately 94% had an Eastern Cooperative Oncology Group performance status of 0 or 1. Gastrointestinal malignancies were the most common, reflecting referral patterns and disease prevalence. On average, participants had close to six previous treatments, including 3.7 systemic therapies, 1.3 surgeries, and 0.6 radiation treatments. There was an average of 2.0 months between finishing previous treatment and starting a phase I study agent, and 3.4 years between cancer diagnosis and starting a phase I study.

Treatment outcomes. As described in Methods, two analyses were conducted: one including all participants (n = 683) and another excluding those at doses greater than the MTD (n = 588). Radiographic responses and treatment-induced toxicities are reported from 3 to 12 months after starting treatment (Fig. 1), given that the first planned imaging on most studies occurred after two cycles of treatment (cycles lasted on average for 3-4 weeks).

With regard to favorable treatment outcomes, in each of the two analyses, the percentage of patients whose disease was stable or better (indicating controlled disease) and who remained on treatment (indicating absent or tolerable side effects) was greater in the low-dose group than in the medium- and high-dose groups at 90 days, albeit not statistically significant, and the percentage remained comparable up to 1 year after starting therapy (Fig. 1A).

Published OnlineFirst February 15, 2010; DOI: 10.1158/1078-0432.CCR-09-2684

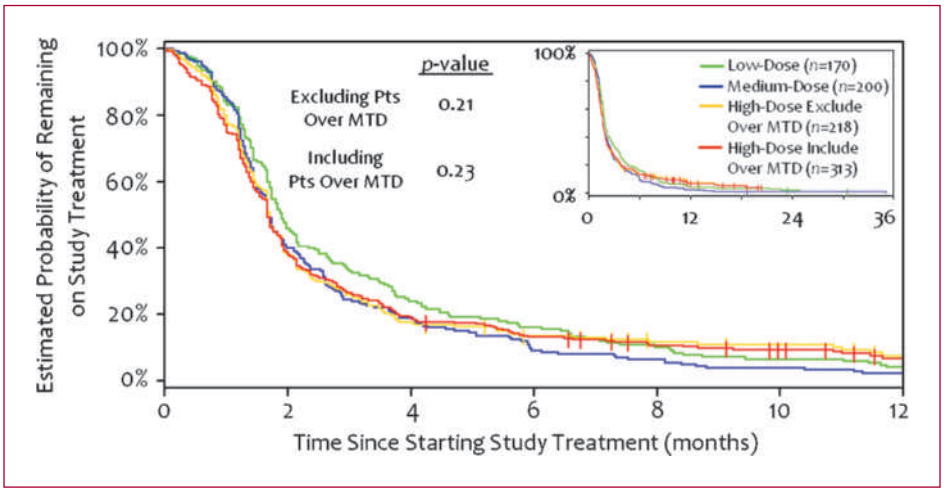

Fig. 2. Kaplan-Meier estimate of time-to-treatment failure. Tick marks, censored patients (those still on study on June 30, 2008, the last date included in this analysis). *P* values are for low-, medium-, and high-dose groups. Inset, 3-y data.

For example, the percentage of patients with complete response/partial response/stable disease and who were still on therapy at 90 days was 32.9% versus 25.2% for low- versus high-dose groups, even when patients treated above the MTD are excluded ($P = 0.08$).

About unfavorable outcomes, the percentage of patients who came off trial for toxicity was lowest in the low-dose group and highest in the high-dose group at all time points, even if patients treated above the MTD were excluded. For example, these percentages are 1.8% versus 9.3% ($P < 0.01$) at 3 months and 2.4% versus 11.4% ($P < 0.01$) at 12 months (Fig. 1B). When patients treated above the MTD were included, the particularly large percentage of patients in the high-dose group who came off for toxicity (16.2% by 365 days) can be attributed to the fact that this group contained 95 patients treated at doses above the MTD. Other than toxicities, some patients came off study because of disease progression. Patients did not fail treatment more often in the low-dose group than in the medium or high-dose groups (for example, progressive disease or toxicity at 3 months in 58.2% versus 65.9% of patients for low- versus high-dose group when those treated over the MTD are excluded; $P = 0.12$; Fig. 1C). A small percentage of patients (~10% in each dose group; data not shown) came off study for nondisease- and nontreatment-related reasons such as comorbidities and personal issues. In time-to-treatment failure analysis, these patients are still considered failures at the time drug was discontinued.

Time-to-treatment failure, progression-free survival, overall survival. Time-to-treatment failure, progression-free survival, and overall survival were estimated by the Kaplan-Meier method and were found to be similar for low-, medium-, and high-dose groups in analysis of all participants and in the analysis that excludes participants treated above the MTD. In fact, in no case does the low-dose group have a less desirable outcome than the medium- or high-dose groups (Figs. 2–4). For all participants, median time-to-treatment failure was 1.7 months (Fig. 2) and median progression-free survival was 1.9 months (Fig. 3). Median overall survival was 8.2 months for all

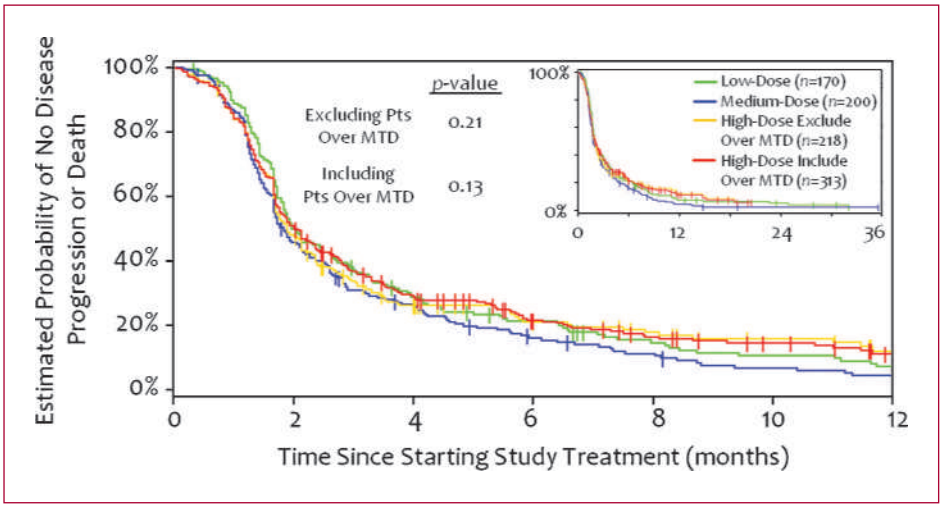

Fig. 3. Kaplan-Meier estimate of progression-free survival. Tick marks, patients who started another treatment before disease progression or death or who were on study on June 30, 2008. *P* values are for low-, medium-, and high-dose groups. Inset, 3-y data.

Published OnlineFirst February 15, 2010; DOI: 10.1158/1078-0432.CCR-09-2684

participants (Fig. 4), consistent with published data (24). Of note is that, upon restaging, a best response of stable disease, partial response, or complete response was observed in 46.8% of patients (first restaging on most studies occurs after two cycles of treatment, with cycles lasting 3-4 weeks). Stable disease for at least 6 months, partial response, or complete response was observed in 11.9% of patients.

Discussion

The practice of administering maximum tolerated drug doses to oncology patients originates from studies on childhood leukemia. Preclinical studies showed that drug dose was proportional to the percentage of leukemic cells killed (16), and the first clinical trial showing increased benefit with higher dose therapy was published more than four decades ago (17). Although the practice of treating at or near the MTD has generally been maintained, the practical mechanics of how that dose is determined, specifically in phase I trials, is an issue of debate. Ethicists raise concerns over a large percentage of patients on phase I oncology trials receiving study drugs at potentially subtherapeutic doses until the vicinity of the MTD is achieved (10, 12–14).

To address this concern, we evaluated dose-response outcomes of 683 participants in 24 contemporary phase I oncology studies (conducted between 2004 and 2008; Methods). We included all consecutive studies in the specified time frame (Methods) to best capture the outcomes of all-comers to contemporary phase I studies, as opposed, for example, to including only single-agent studies. Greater than 97% of study participants received at least one targeted agent (Table 1). As such, our results may primarily be helpful in the context of evaluating trials studying similar agents, given that this study cannot draw conclusions about relative outcomes for patients receiving lower versus higher doses of classically cytotoxic chemotherapy. We found that participants treated in low-dose cohorts of contemporary phase I studies are not clinically disadvantaged compared with their higher-dose counterparts (Figs. 1–4). This is consistent with data from another analysis in a smaller group of patients (25). Furthermore, advantageous effects were observed for the low-dose group with regard to the percentage of participants that came off trial for toxicity, even when patients treated above the MTD were excluded (2.4% versus 11.4% for low- versus high-dose at 1 year; $P < 0.01$; Fig. 1B). Consistent with this, one analysis of 149 phase I studies showed that trials with more aggressive dose escalation schemes had greater toxicities while response rates remained similar (26).

About dose groups, they were arbitrarily set to reasonable ranges (low, ≤25% of MTD; medium, 25-75% of MTD; and high, ≥75% of MTD; Methods). However, to further examine the relationship, another analysis was done. Comparison of participants treated (*a*) below the MTD ($n = 393$) versus (*b*) at the MTD (or maximum tested dose if no MTD was found; $n = 195$) showed no discernable downside to being treated at the lower doses with regard to the described outcomes. For example, comparison of patients treated below the MTD versus those treated at the MTD (or maximum tested dose if no MTD was found) showed 29.0% versus 23.1% of patients had complete response/partial response/stable disease and were on therapy at 3 months ($P = 0.12$), and 13.0% versus 9.2% had complete response/partial response/stable disease and were on therapy at 6 months ($P = 0.16$). Further studies will be required to elucidate the basis for this observation, but it is possible that targeted agents exert their effects in a relatively dose-independent manner or that even the lowest doses in contemporary phase I oncology studies are above a minimum threshold for affecting the target.

In evaluating the data, it is somewhat surprising that the low-dose group outcomes were as favorable as those of the high-dose group, given that the high-dose group is enriched with patients more likely to respond to

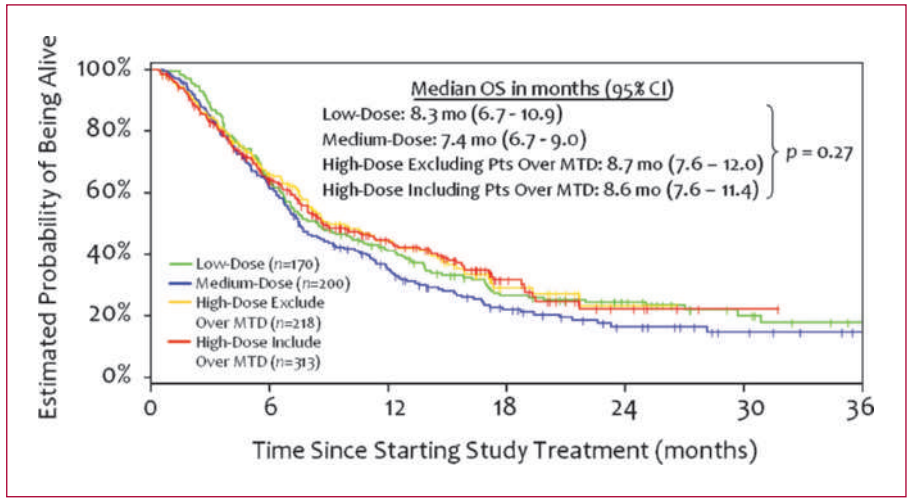

Fig. 4. Kaplan-Meier analysis of overall survival. Overall survival for up to 3 y after starting phase I study.

Published OnlineFirst February 15, 2010; DOI: 10.1158/1078-0432.CCR-09-2684

Table 1. Characteristics of trials included for analysis

Trial target/mechanism	Class	No. of patients per trial (n = 683)	No. of patients treated above MTD (n = 95)	No. of dose levels tested
Single agent				
Angiopoietin inhibitor	Biologic	17	0	4
Apoptosis	Biologic	35	0	4
Aurora kinase inhibitor	Small molecule	16	0	9
Cyclin-dependent kinase inhibitor	Small molecule	18	4 (22%)	5
Death receptor	Biologic	23	0	5
DNA synthesis inhibitor	Small molecule	16	0	4
EGFR/VEGFR inhibitor	Small molecule	11	2 (18%)	6
Hypomethylating agent	Small molecule	31	0	5
Insulin growth factor receptor	Biologic	21	0	4
Mitotic inhibitor	Small molecule	18	5 (28%)	8
Multikinase inhibitor	Small molecule	11	2 (18%)	3
NF-κB inhibitor	Small molecule	21	3 (14%)	10
Ras inhibitor	Small molecule	24	0	5
STAT-3 inhibitor	Small molecule	24	0	5
Tyrosine kinase inhibitor	Small molecule	49	15 (31%)	13
Topoisomerase inhibitor	Small molecule	14	0	5
Multiple mechanisms, apoptosis inducer/antiangiogenic	Small molecule	40	8 (20%)	8
Multiple mechanisms, apoptosis inhibitor/tubulin inhibitor	Small molecule	11	0	4
Two agents				
Antiangiogenic + proteosome inhibitor	Biological + small molecule	54	0	9
Hypomethylating agent + HDAC inhibitor	Small molecule	68	6 (10%)	7
Immune + multiple mechanisms, including Src inhibitor	Immune modulator + small molecule	20	7 (35%)	5
Microtubule inhibitor + proapoptotic	Small molecule	33	8 (24%)	7
Ras inhibitor + multikinase inhibitor	Small molecule	58	14 (24%)	5
Three agents				
Proteosome + DNA synthesis inhibitors	Small molecule	50	21 (42%)	9

Abbreviations: EGFR, epidermal growth factor receptor; HDAC, histone deacetylase; STAT-3, signal transducer and activator of transcription 3; VEGFR, vascular epithelial growth factor receptor.

therapy. This enrichment exists because, if a treatment shows promising results in a patient(s) during the dose-escalation phase of a study, then the study may allow for additional patients who have the same tumor type(s) as the one(s) who responded to be enrolled at the MTD (or maximum tested dose). Fourteen of the 24 studies in this analysis include patients treated in such MTD dose-expansion cohorts. The most likely explanation for this surprising result may be that patients treated at the MTD, which is defined based upon toxicities observed within the first 3 to 4 weeks of treatment, had more cumulative toxicities with prolonged administration than those treated at lower doses, thus necessitating their withdrawal. In addition, while a higher dose can cause greater toxicity, it does not necessarily result in greater efficacy; targeted agents may fully modulate their target or have distinct activities at doses lower than the MTD. Such a precedent has been shown for decitabine, an agent used to treat myelodysplastic syndrome, which is better tolerated and more effective at lower doses (27–29). Collectively, these observations suggest that the issue of optimum dosing of targeted therapies is complex and that exploring doses lower than the MTD may be worthwhile for some agents. Consistent with this notion, a discussion of the prudence of the classic MTD approach in the era of targeted therapies is taking place (30–32). Some argue that too little is known to abandon historical approaches (33), whereas others argue that efforts should be made to guide treatment

Published OnlineFirst February 15, 2010; DOI: 10.1158/1078-0432.CCR-09-2684

based on the minimal effective dose (34) or optimum biological dose (35, 36).

Finally, although the aim of this study was to evaluate potential downsides to low-dose cohort participants on phase I oncology studies and not to evaluate the efficacy of phase I studies, the latter point deserves some mention. Disease response rates seen in this analysis are consistent with previously published results (2, 37–40). For example,

Table 2. Baseline patient characteristics

	Low dose*	Medium dose*	High dose*		*P*	
	≤25% of MTD (*n* = 170)	25-75% of MTD (*n* = 200)	75-100% MTD (exclude patients treated over MTD) *n* = 218	≥75% of MTD (include patients treated over MTD) *n* = 313	Exclude patients over MTD†	Include patients over MTD‡
Age (y; mean ± SD)‡‡	55.8 ± 12.9	55.1 ± 14.0	56.1 ± 12.9	56.0 ± 13.8	0.79	0.74
Sex (%)					0.54	0.53
Male	58.2	52.5	56.0	55.3		
Female	41.8	47.5	44.0	44.7		
Race (%)					0.69	0.60
White	77.1	74.5	80.3	80.5		
Black	9.4	11.0	6.9	6.4		
Hispanic	9.4	9.0	6.9	8.0		
Asian	4.1	4.5	4.6	3.8		
Other	0.0	1.0	1.4	1.3		
Performance status (%; PS)					0.55	0.78
Patients with PS = 0	32.9	30.0	31.2	31.6		
Patients with PS = 1	60.6	66.0	63.8	61.0		
Patients with PS ≥ 2	6.5	4.0	5.0	7.3		
Tumor type (%)§					0.32	0.73
Breast (*n* = 61)	7.1	11.5	8.7	8.3		
Gastrointestinal (*n* = 206)	37.6	31.0	29.4	25.6		
Genitourinary (*n* = 63)	7.1	8.0	9.6	11.2		
Head and neck (*n* = 50)	7.6	6.0	8.3	8.0		
Melanoma (*n* = 60)	7.6	9.0	7.8	9.3		
Thoracic (*n* = 54)	9.4	6.5	6.9	8.0		
All others (*n* = 189)	23.5	28.0	29.4	29.7		
Number of previous treatments (mean ± SD)‡‡					0.11‖	0.13‖
Systemic treatments	3.8 ± 2.2	3.9 ± 2.3	3.5 ± 2.4	3.5 ± 2.4		
Radiation treatments	0.6 ± 0.8	0.6 ± 0.8	0.7 ± 0.8	0.7 ± 0.9		
Surgical treatments	1.2 ± 1.2	1.4 ± 1.4	1.3 ± 1.0	1.3 ± 1.1		
Other treatments¶	0.2 ± 0.6	0.3 ± 1.0	0.2 ± 0.5	0.2 ± 0.5		
	5.8 ± 2.8	6.2 ± 2.7	5.7 ± 2.8	5.7 ± 2.8		
Time from cancer diagnosis to C1D1 of study treatment**	3.2 (0.4-26.6)	3.5 (0.3-33.1)	3.1 (0.1-36.7)	3.4 (0.1-36.7)	0.79	0.63
Time from end of last treatment to C1D1 of trial†† (mo; median with range)	1.7 (0.3-34.9)	2.0 (0.3-67.4)	2.1 (0.0-269.9)	2.1 (0-269.9)	0.10	0.10

*As per Methods, dose percentage is percentage of MTD or percentage of maximum tested dose if the maximum tested dose was not a MTD.

†*P* values for analyses of low-, medium-, and high-dose exclude patients over MTD (*n* = 588).

‡*P* values for analyses of low-, medium-, and high-dose include patients over MTD (*n* = 683).

§*n* values include all patients. All others include endocrine, gynecological, lymphoma, myeloma, sarcoma, and other malignancies.

‖Given *P* values are for the cumulative number of treatments by one way ANOVA.

¶Concurrent chemotherapy and radiation therapy is categorized as other treatments.

**C1D1 = cycle 1, day 1 of phase I treatment.

††Two patients (both in the high-dose group) had no therapy before phase I treatment.

‡‡SD = standard deviation.

Published OnlineFirst February 15, 2010; DOI: 10.1158/1078-0432.CCR-09-2684

Hortsmann et al. (39) evaluated 460 phase I trials enrolling 11,935 participants from 1991 to 2002, of whom 10,402 (87.2%) were evaluated for response (41). A best response of complete response or partial response was observed in 10.6% of participants, whereas an additional 34.1% had stable disease, for an overall "benefit rate" of 44.7%. In our study, 622 (91.1%) of 683 participants were evaluated for response, whereas 8.9% came off study for toxicities or for other reasons before a first assessment of disease response. Of participants evaluated, 46.8% achieved a best response of complete response, partial response, or stable disease, which is similar to the Hortsmann study. In addition, in our study, 11.9% of patients achieved complete response, partial response, or prolonged stable disease (prolonged stable disease = stable disease for ≥6 months).

The ethical issues surrounding phase I trials are complex and may benefit from data gleaned through investigational analyses. In this study, we evaluated a large cohort of patients participating in contemporary phase I oncology trials of predominantly targeted agents. We found no discernable downside to being treated in the low- versus the medium- or high-dose groups. These data may help to alleviate concerns about a relative lack of benefit for patients in low-dose cohorts of phase I trials and support the notion that further investigation of targeted agents may be required to fully understand their optimal dosing and potentially beneficial effects.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

We thank Drs. Steve Lockless and Richard Theriault for critical article review and Dr. Fadi Braiteh and Karin Hahn for discussions about conceptual design of the study.

Grant Support

Grant RR024148 from the National Center for Research Resources, a component of the NIH Roadmap for Medical Research (http://nihroadmap.nih.gov/clinicalresearch/overview-translational.asp; R. Kurzrock), and by grant CA16672 from the National Cancer Institute (J.J. Lee).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received 10/5/09; revised 11/12/09; accepted 11/14/09; published OnlineFirst 2/9/10.

References

1. American Society of Clinical Oncology. Critical role of phase I clinical trials in cancer treatment. J Clin Oncol 1997;15:853–9.
2. Von Hoff DD, Turner J. Response rates, duration of response, and dose response effects in phase I studies of antineoplastics. Invest New Drugs 1991;9:115–22.
3. Eisenhauer EA, O'Dwyer PJ, Christian M, Humphrey JS. Phase I clinical trial design in cancer drug development. J Clin Oncol 2000;18:684–92.
4. Rogatko A, Babb JS, Tighiouart M, Khuri FR, Hudes G. New paradigm in dose-finding trials: patient-specific dosing and beyond phase I. Clin Cancer Res 2005;11:5342–6.
5. Daugherty CK. Ethical issues in the development of new agents. Invest New Drugs 1999;17:145–53.
6. Markman M. The needs of science vs the needs of patients: ethical concerns in cancer clinical trials. Cleve Clin J Med 2003;70:1008–9, pp. 13-4, 16.
7. Meropol NJ, Weinfurt KP, Burnett CB, et al. Perceptions of patients and physicians regarding phase I cancer clinical trials: implications for physician-patient communication. J Clin Oncol 2003;21:2589–96.
8. Daugherty C, Ratain MJ, Grochowski E, et al. Perceptions of cancer patients and their physicians involved in phase I trials. J Clin Oncol 1995;13:1062–72.
9. Markman M. Assessing cancer clinical trials: will your patient benefit from a 'breakthrough'? Cleve Clin J Med 2002;69:368–9, pp. 75-6.
10. Angelos P. Ethical issues in cancer patient care. 2nd ed. Springer; 1999.
11. Chen EX, Tannock IF. Risks and benefits of phase 1 clinical trials evaluating new anticancer agents: a case for more innovation. JAMA 2004;292:2150–1.
12. Ratain MJ, Mick R, Schilsky RL, Siegler M. Statistical and ethical issues in the design and conduct of phase I and II clinical trials of new anticancer agents. J Natl Cancer Inst 1993;85:1637–43.
13. Lipsett MB. On the nature and ethics of phase I clinical trials of cancer chemotherapies. JAMA 1982;248:941–2.
14. Joffe S, Miller FG. Rethinking risk-benefit assessment for phase I cancer trials. J Clin Oncol 2006;24:2987–90.
15. Dunn S. Steve's strategic guide to phase I cancer clinical trials. 2004, cited; Available from: http://www.cancerguide.org/trials_phase1.html.
16. Skipper HE, Schabel FR, Wilcox WS. Experimental evaluation of potential anticancer agents. XII. On the criteria and kinetics associated with "curability" of experimental leukemia. Cancer Chemother Rep 1964;35:1–111.
17. Pinkel D, Hernandez K, Borella L, et al. Drug dosage and remission duration in childhood lymphocytic leukemia. Cancer 1971;27:247–56.
18. Henderson IC, Hayes DF, Gelman R. Dose-response in the treatment of breast cancer: a critical review. J Clin Oncol 1988;6:1501–15.
19. Bonadonna G, Valagussa P. Dose-response effect of adjuvant chemotherapy in breast cancer. N Engl J Med 1981;304:10–5.
20. Pratt WB, Ruddon RW, Ensminger WD, Maybaum J. The anticancer drugs. 2nd ed. Oxford University Press; 1994.
21. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer 1981;47:207–14.
22. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205–16.
23. Jiang H, Fine JP. Survival analysis. Methods Mol Biol 2007;404:303–18.
24. Wheler J, Tsimberidou AM, Hong D, et al. Survival of patients in a Phase 1 clinic: the M. D. Anderson Cancer Center Experience. Cancer 2009;115:1091–9.
25. Postel-Vinay S, Arkenau HT, Olmos D, et al. Clinical benefit in phase-I trials of novel molecularly targeted agents: does dose matter? Br J Cancer 2009;100:1373–8.
26. Koyfman SA, Agrawal M, Garrett-Mayer E, et al. Risks and benefits associated with novel phase 1 oncology trial designs. Cancer 2007;110:1115–24.

Published OnlineFirst February 15, 2010; DOI: 10.1158/1078-0432.CCR-09-2684

27. Jabbour E, Issa JP, Garcia-Manero G, Kantarjian H. Evolution of decitabine development: accomplishments, ongoing investigations, and future strategies. Cancer 2008;112:2341–51.
28. van Groeningen CJ, Leyva A, O'Brien AM, Gall HE, Pinedo HM. Phase I and pharmacokinetic study of 5-aza-2'-deoxycytidine (NSC 127716) in cancer patients. Cancer Res 1986;46:4831–6.
29. Wijermans P, Lubbert M, Verhoef G, et al. Low-dose 5-aza-2'-deoxycytidine, a DNA hypomethylating agent, for the treatment of high-risk myelodysplastic syndrome: a multicenter phase II study in elderly patients. J Clin Oncol 2000;18:956–62.
30. Parulekar WR, Eisenhauer EA. Phase I trial design for solid tumor studies of targeted, non-cytotoxic agents: theory and practice. J Natl Cancer Inst 2004;96:990–7.
31. Seymour L. The design of clinical trials for new molecularly targeted compounds: progress and new initiatives. Curr Pharm Des 2002;8:2279–84.
32. Hoekstra R, Verweij J, Eskens FA. Clinical trial design for target specific anticancer agents. Invest New Drugs 2003;21:243–50.
33. Sleijfer S, Wiemer E. Dose selection in phase I studies: why we should always go for the top. J Clin Oncol 2008;26:1576–8.
34. Haines IE. Dose selection in phase I studies: why we should always go for the most effective. J Clin Oncol 2008;26:3650–2, author reply 2-3.
35. Fox E, Curt GA, Balis FM. Clinical trial design for target-based therapy. Oncologist 2002;7:401–9.
36. Wolf M, Swaisland H, Averbuch S. Development of the novel biologically targeted anticancer agent gefitinib: determining the optimum dose for clinical efficacy. Clin Cancer Res 2004;10:4607–13.
37. Decoster G, Stein G, Holdener EE. Responses and toxic deaths in phase I clinical trials. Ann Oncol 1990;1:175–81.
38. Estey E, Hoth D, Simon R, Marsoni S, Leyland-Jones B, Wittes R. Therapeutic response in phase I trials of antineoplastic agents. Cancer Treat Rep 1986;70:1105–15.
39. Horstmann E, McCabe MS, Grochow L, et al. Risks and benefits of phase 1 oncology trials, 1991 through 2002. N Engl J Med 2005;352:895–904.
40. Roberts TG, Jr., Goulart BH, Squitieri L, et al. Trends in the risks and benefits to patients with cancer participating in phase 1 clinical trials. JAMA 2004;292:2130–40.
41. Kurzrock R, Benjamin RS. Risks and benefits of phase 1 oncology trials, revisited. N Engl J Med 2005;352:930–2.

Published OnlineFirst February 15, 2010; DOI: 10.1158/1078-0432.CCR-09-2684

Clinical Cancer Research

Phase I Oncology Studies: Evidence That in the Era of Targeted Therapies Patients on Lower Doses Do Not Fare Worse

Rajul K. Jain, J. Jack Lee, David Hong, et al.

Clin Cancer Res 2010;16:1289-1297. Published OnlineFirst February 15, 2010.