

Are Doses and Schedules of Small-Molecule Targeted Anticancer Drugs Recommended by Phase I Studies Realistic?

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Abstract

Tolerability of molecularly targeted agents (MTA) used in cancer therapeutics is determined in phase I trials. We reviewed the reported incidence of toxicity in phase III trials at doses and schedules recommended by phase I trials to evaluate whether these recommendations are realistic when drugs are used in larger populations of patients. We systematically reviewed a safety profile of small molecule (SM-MTA) and mAb MTA (MA-MTA) approved by the FDA in the last 12 years. There was a significantly increased percentage of grade 3 or 4 adverse events reported with SM-MTA compared with MA-MTA [40% vs. 27%; RR 1.5; 95% confidence interval (CI), 1.10–2.25, $P = 0.038$] in phase III studies. Importantly, a substantial proportion of patients (45%) treated with SM-MTA required dose modifications due to drug-related toxicity in phase III trials. However,

this toxicity was associated to a definitive study drug discontinuation in only 9%. Overall, 25% of SM-MTA declared recommended phase II doses below MTD based on pharmacokinetic–pharmacodynamic data and these trials were associated with a significantly reduced number of dose modifications in registration trials (32% vs. 50%; RR 0.64; 95% CI, 0.43–0.88, $P = 0.01$). Tolerability is going to come into further focus due to the need for combinations of SM-MTA and other anticancer agents. There was a higher incidence of grade 3–4 toxicity in phase III trials in combinations versus single-agent SM-MTAs (64% vs. 37%; RR 1.73; 95% CI, 1.3–2.3, $P = 0.001$). These results indicate that phase I studies underestimate toxicity while recommending doses of SM-MTA. *Clin Cancer Res*; 22(9); 2127–32. ©2015 AACR.

Introduction

The latter half of the 20th century focused on developing effective anticancer drug targeting DNA or microtubules. Though effective, these drugs have a narrow therapeutic index and are often collectively called chemotherapy. The last decade has focused on developing drugs not targeting DNA or microtubules directly within cancer cells that are often loosely termed as molecularly targeted agents (MTA). These agents have been developed to selectively affect the tumor or supporting vasculature and are thought to have a better therapeutic index compared with chemotherapy. MTAs can be mAbs (MA-MTA) or chemical entities with molecular mass of approximately 500 daltons or lower often called small molecules (SM-MTA). We reviewed 90 oncology products for 178 indications granted approval by the FDA during the last 12 years of drug development (1).

The process of clinical drug development starts with phase I clinical trials (2–4). The main purpose of a phase I trial is to recommend the appropriate dose and schedule (RP2D) of a novel

anticancer drug by characterizing the pharmacokinetic and pharmacodynamic profile of a new drug or drug combination. The RP2D is crucial as it is used to design and conduct future trials of that novel agent.

A RP2D that is too low risks the drug having lack of efficacy in future clinical trials; however, a dose that is too high risks excessive toxicity (5, 6). Researchers using an exhaustive retrospective analysis have shown that a substantial proportion of clinically relevant toxicities found in registration trials were previously described in early trials. This review included data studying MTAs and conventional cytotoxics which have very different therapeutic indices and crucially did not comment on the tolerability of targeted agents in phase III clinical trials (7).

We aimed to investigate whether the RP2D of new MTAs were not tolerable in phase III studies. The tolerability of the drugs in phase III studies influences efficacy endpoints and its use in the community after registration. To study a homogenous group of drugs, we excluded drugs targeting the immune checkpoints and newer DNA/tubulin-targeting agents. We reviewed the last 12 years of FDA oncology approvals from 2002 to 2015. We performed an evaluation of tolerability of each MTA, focusing specially on dose modifications (either dose interruptions or dose delays) due to drug toxicities in phase III setting and benchmark this against the RP2D derived from phase I trials.

Materials and Methods

Data sources

To identify FDA-approved drugs and indications from 2002 to 2015, we searched documents stored on the CDER database Drugs@FDA.

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (<http://clincancerres.aacrjournals.org/>).

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Translational Relevance

Phase I studies are done to recommend doses and schedules of anticancer drugs to be used for future development. The doses and schedules are determined by taking into account toxicity, pharmacokinetics, and pharmacodynamics in a relatively small number of patients. This analysis shows a high incidence of toxicity is seen with small-molecule molecularly targeted agents in late-phase clinical trials based on the doses and schedules recommended in phase I studies. Refinement of our current methodology of recommending phase II doses in phase I studies are needed.

Afterward, we performed an electronic search of Pubmed, ClinicalTrials.gov, and American Society of Clinical Oncology (ASCO) abstract databases. For each targeted agent, the name of the drug, phase I, and phase III trial were included to find relevant studies published prior to February, 2015. We did not restrict the beginning date. An average of 534 hits per drug were obtained (110–958). Finally, the references of eligible studies and relevant review articles were screened.

Study selection

MTAs for the treatment of solid and hematologic malignancies approved by the FDA from 2002 to 2015 were selected. Pediatric anticancer drugs, drugs targeting DNA or microtubules directly, and immune checkpoint–modulating agents were excluded.

Two reviewers (D. Roda and B. Jimenez) assessed publications involving these group of targeted agents, prioritizing phase I clinical trials, and phase III trials involved on their final approval. Other potential phase II or III studies could also be reviewed if they were considered as potentially relevant. Finally, the main conclusions were assessed by a third reviewer (U. Banerji).

Parameters assessed

The current analysis studied dose interruptions and dose reductions in MTAs in phase III studies and compared this with the RP2D generated from phase I studies. All toxicities reported in phase I and phase III studies used NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE) reporting. We defined dose modification as a frequent occurrence ($\geq 30\%$) or not.

We also studied the phase I trials to see whether pharmacodynamic studies were done at the R2PD and whether a pharmacodynamically active range of dose levels was identified so as to guide dose interruptions and reductions in future phase III studies.

Statistical analysis

Toxicity correlations were summarized using descriptive statistics. Proportions from independent groups were compared using the χ^2 test. All the statistical analyses were performed using SPSS version 20.00.

Results

Between January 1, 2002 and February 1, 2015, the FDA granted approval to 90 oncology products for 178 indications. From this group of new drugs, a number of 34 MTAs were

included in our analysis. A total of 130 articles and abstracts were assessed according to our predefined inclusion criteria to accurately describe the safety profile of each drug (Fig. 1).

Eighty-six percent of SM-MTAs were developed in phase III trials with exactly the same dose and schedule that was defined as RP2D in early phase I trials.

There was a significantly increased percentage of grade 3 or 4 NCI-CTCAEs reported with SM-MTA compared with MA-MTA [40% vs. 27%; RR 1.5; 95% confidence interval (CI), 1.10–2.25, $P = 0.038$]. Interestingly, 88.4% (23/26) of trials involving target antibodies did not describe details of dose modifications and dose reductions. Furthermore, a majority of MA-MTAs were developed and finally approved in combination with classic chemotherapy 69% (18/26), and tolerance of antibody–chemotherapy combinations was not significantly different compared with chemotherapy alone; grade 3–4 toxicity reported as a single agent and in combination was 61% versus 68%, respectively (RR 1.10; 95% CI, 0.89–1.81, $P = 0.37$).

In contrast, of all FDA-registered SM-MTAs included in these cohorts, 45% of patients in phase III studies required dose adjustments. This was due to dose interruptions in 48% and dose reductions in 41.2%. However, only 9% of patients finally required a dose discontinuation due to drug-related toxicity (Figs. 2 and 3).

In contrast with targeted antibodies, only 5/50 (10%) of SM-MTAs were evaluated in combination with classic chemotherapy, hormone therapy, or other MTAs in phase 3 trials. There was a statistically significant increased rate of grade 3–4 toxicities described for combination trials involving SM-MTA compared with single-agent small molecules (64% vs. 37%; RR 1.73, 95% CI, 1.3–2.3, $P = 0.001$). However, dose modifications or discontinuations needed did not differ significantly between them (45% vs. 46% and 8% vs. 15%; RR 1.0; 95% CI, 0.7–1.4, $P = 0.89$; RR 0.6; 95% CI, 0.2–1.1, $P = 0.12$, respectively).

Of note, of the phase I studies evaluated, a majority 57% (16/28) did not have details of dose modifications on study; in contrast, 66% (33/50) of registration trials did describe dose interruptions and reductions related to the study drug (Supplementary Table S1).

Overall 21/28 (75%) of MTAs declared the MTD and R2PD as the same dose. Interestingly, phase III trials which had RP2D in phase I studies declared on the basis of pharmacokinetic and pharmacodynamic data and had a RP2D lower than the MTD and had a significantly reduced percentage of dose modifications compared with those trials where the RP2D and MTD were the same. (32% vs. 50%; RR 0.64; 95% CI, 0.43–0.88, $P = 0.01$).

Discussion

MTAs often display a different toxic profile from conventional chemotherapy. Toxicities tend not to be life-threatening events, such as neutropenia, however, are often chronic and significantly affect the quality of life of patients. Several publications have discussed concordance of toxicity in early and late clinical trials of MTAs (7–10). Jardim and colleagues in a recent publication concluded that early trials could accurately predict a safety profile of new cancer drugs. Focus is on the fact that most common side effects described in registration trials were previously accurately described in phase I trials. Moreover, they also concluded that the final approved dose was within 20% of the RP2D in the majority of trials assessed (7). However, this analysis combined MTAs and

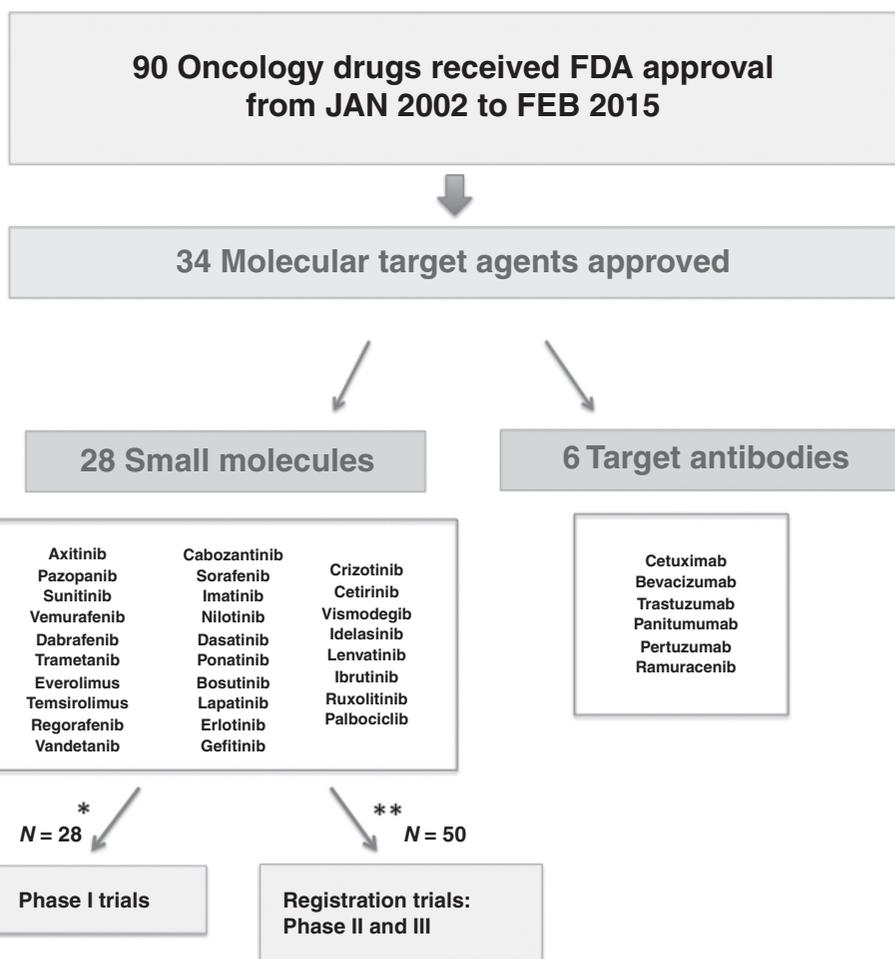


Figure 1.

MTAs included in our analysis. * 32% of phase I trials with MTA described information regarding dose interruptions, or reductions (42%), or dose discontinuations (60%). ** 66% of phase III trials with MTA reported information regarding dose interruptions, or reductions (74%) or dose discontinuations (96%).

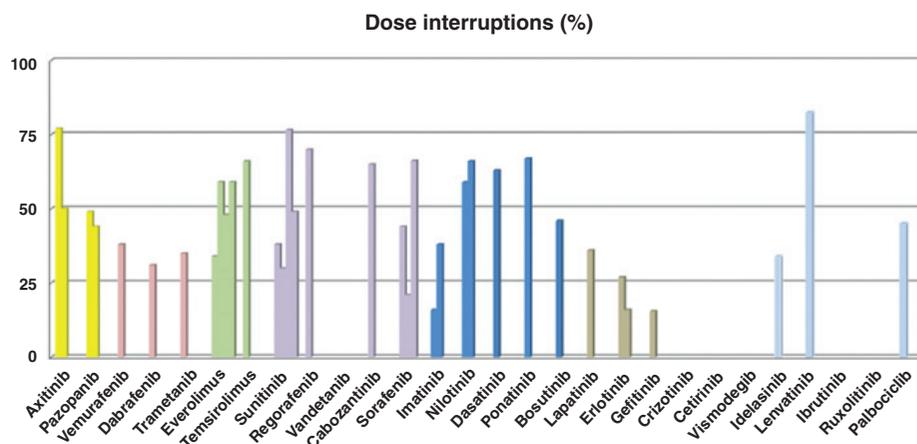
chemotherapeutic agents. It is well known that conventional chemotherapeutic agents have their R2PD defined by MTD and thus this analysis pooling MTAs and conventional cytotoxic agents could give rise to a biased result showing that R2PDs of MTAs are accurate and predict toxicities in phase III studies.

In contrast, our findings focused only on MTAs and thus found 48% of patients treated with small molecules required dose modification in phase III studies. There are multiple reasons for

this. First, as previously published by Postel-Vinay, the relevance of chronic toxicities, almost 20% of patients treated within phase I trials with new MTA required significant reductions in dose intensity at any time during their treatment (9). Therefore, they proposed a new modification of the classical definition of MTD, suggesting that recommended phase II dose assessment should incorporate all available information from any cycle including less severe toxicities (such as grade 1–2 toxicities) leading to dose

Figure 2.

Incidence of dose interruptions of SM-MTA in phase III studies.



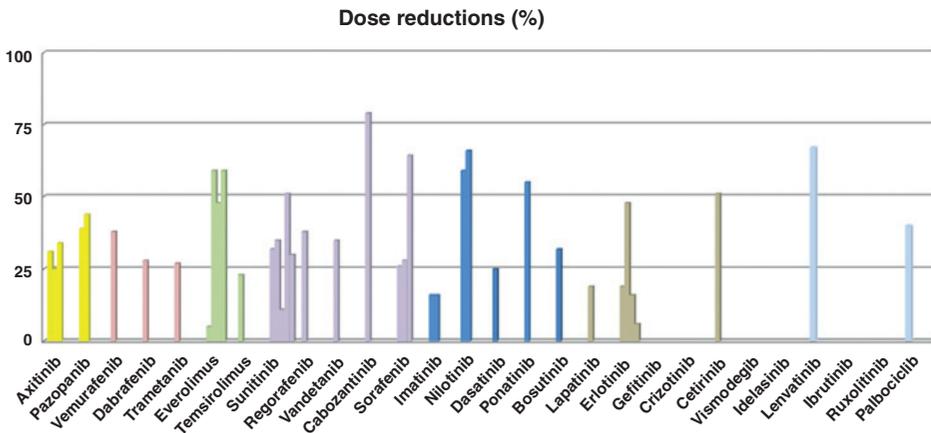


Figure 3. Incidence of dose reductions of SM-MTA in phase III studies.

modifications (7–9). We endorse this view and strongly recommend studying toxicity for at least 2 cycles in the expansion cohort of phase I trials.

While collecting the data for this current article, we could only find the timing of dose reductions/interruptions in 1 of 50 phase III trials of small molecules. This information would have helped future correlations of toxicities timing between phase I and III studies. Therefore, we suggest that the cycle at which dose interruptions and delays occurred should be documented in toxicity tables while reporting phase III trials.

In addition to these suggestions, we propose that the RP2D should be explored in at least 12 patients rather than the current practice of treating 6 patients and this may help in defining a RP2D that is more likely to be tolerable in phase III studies. This would concur with options of other groups who have studied expansion cohorts (8); however, in contrast with others, we have exclusively studied MTAs not including cytotoxic agents. Moreover, phase I expansions are increasingly being conducted in specific patient subgroups and the toxicities recorded from these patients could be used for this purpose.

Importantly, chronic grade 2 toxicities are the cause of dose modifications. (9) We recommend that if 30% of patients in a

expansion cohort have given dose modifications due to any grade toxicity, the dose is considered as nontolerable.

This is of particular relevance to MTAs in combination studies. Recently, as an example of combination toxicity, Rugo and colleagues reported the incidence and time course of everolimus-related events in Bolero-2 trial. Remarkably, 62% of patients treated in everolimus arm required dose interruptions/reductions due to toxicity (50).

An interesting finding in our analysis was that small molecules that had MTD as the R2PD had more of chance of dose modifications. Only 7/28 (25%) of phase I trials of small-molecule MTAs recommended a dose below MTD and these studies had a lower incidence of dose modifications. It is difficult to tease out the exact reasons why these decisions were taken; however, the use of robust pharmacokinetic and pharmacodynamic data benchmarked to preclinical models and toxicity past the first cycle of therapy could be reasons why a more realistic RP2D was chosen.

Our results reinforce the challenge of developing small-molecule MTAs as single agents or combinations. If toxicity is dealt with by dose reduction, it is critical to know whether the lower dose is within a pharmacodynamically active range as lowering the dose below that could lead to loss of activity ((Fig. 4). This is

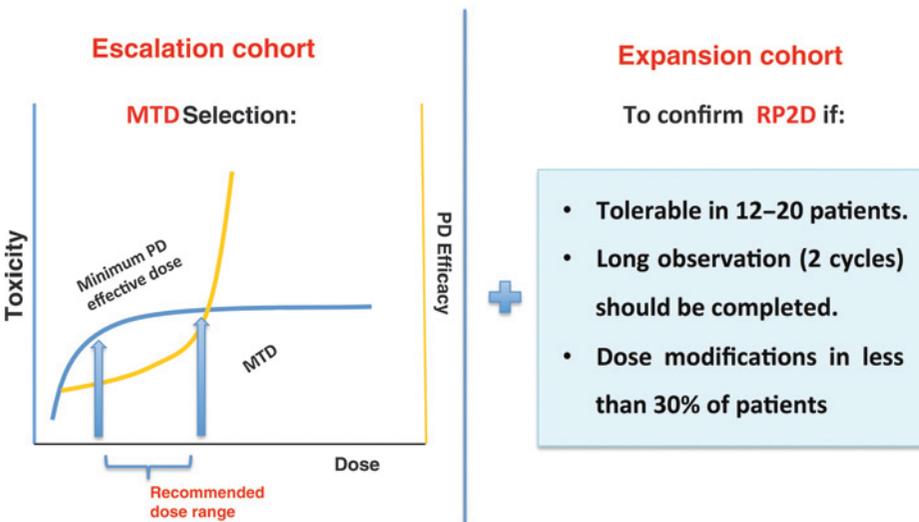


Figure 4. Improved model for reporting tolerated dose in phase I studies.

particularly important in combination studies where preclinical experiments have shown that submaximal dosing of both drugs in a combination might be less effective than a single-agent dose at its maximal pharmacodynamic potential (49). It is crucial that phase I studies report pharmacodynamically active ranges rather than pharmacodynamic effects only at R2PD, as this will equip investigators in later trials with better decision-making tools when choosing between dose reductions or drug holidays (intermittent schedules) in the face of toxicity.

Reassuringly, our data showed that only a minority of patients required a dose discontinuation due to drug-related toxicity in phase III trials and in a majority of cases, dose interruptions or reductions were sufficient to manage drug-related side effects. To conclude this, analysis shows that current phase I studies of SM-MTAs overestimate the R2PD leading to frequent dose modifications in licensed SM-MTAs when used in larger groups of patients. While some drugs truly have a narrow therapeutic index and are destined to have toxicity, exploring intermittent schedules and determining pharmacodynamically active dose ranges can result in RP2Ds that are tolerable in larger populations of cancer patients. Better optimization of dose and schedules leading to

less toxicity will be beneficial for patients and health care providers alike.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: D. Roda, U. Banerji

Development of methodology: D. Roda, U. Banerji

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): D. Roda, B. Jimenez

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): D. Roda, B. Jimenez, U. Banerji

Writing, review, and/or revision of the manuscript: D. Roda, B. Jimenez, U. Banerji

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): D. Roda

Study supervision: D. Roda, U. Banerji

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