Optimal Dosing for Targeted Therapies in Oncology: Drug Development Cases Leading by Example

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Abstract

One of the key objectives of oncology first-in-human trials has often been to establish the maximum tolerated dose (MTD). However, targeted therapies might not exhibit dose-limiting toxicities (DLT) at doses significantly higher than sufficiently active doses, and there is frequently a limited ability to objectively quantify adverse events. Thus, while MTD-based determination of recommended phase II dose may have yielded appropriate dosing for some cytotoxics, targeted therapeutics (including monoclonal antibodies and/or immunotherapies) sometimes need alternative or complimentary strategies to help identify dose ranges for a randomized dose-ranging study. One complementary strategy is to define a biologically efficacious dose (BED) using an "effect marker." An effect marker could be a target engagement, pharmacodynamic, or disease progression marker (change in tumor size for solid tumors or bone marrow blast count for some hematologic tumors). Although the concept of BED has been discussed extensively, we review specific examples in which the approach influenced oncology clinical development. Data extracted from the literature and the examples support improving dose selection strategies to benefit patients, providers, and the biopharmaceutical industry. Although the examples illustrate key contributions of effect markers in dose selection, no one-size-fits-all approach to dosing can be justified. Higher-than-optimal dosing can increase toxicity in later trials (and in clinical use), which can have a negative impact on efficacy (via lower adherence or direct sequelae of toxicities). Proper dose selection in oncology should follow a multifactorial decision process leading to a randomized, dose-ranging study instead of a single phase II dose. 

Introduction

One of the key objectives of oncology first-in-human phase I trials has often been to establish maximum tolerated dose (MTD). While MTD-based determination of the recommended phase II dose (RP2D) may have yielded appropriate dosing for some cytotoxics, targeted therapeutics need alternative or complimentary strategies to help identify dose ranges to take forward in a randomized, dose-ranging study (1–4). This is evident considering that nine oncology drug applications have faced dose optimization as postmarketing requirements or commitments from the FDA (5). A recent example suggesting potential issues with the MTD-based development paradigm is cabozantinib, a multiple tyrosine kinase inhibitor, which was approved at a dose of 140 mg every day, slightly lower than the MTD (175 mg every day) identified in phase I (6). Although lower exposure did not reduce progression-free survival (PFS), higher exposure was associated with earlier dose reduction; at the 140-mg dose 69% of patients had dose holds and 79% of subjects reduced their doses (7, 8). The FDA required a trial comparing the safety and activity of cabozantinib at the approved dose to those at a lower, biologically active dose (9).

The alternative development strategies are also needed because, for many targeted therapies, including monoclonal antibodies (mAb) and/or immunotherapies, dose-limiting toxicities (DLT) may not be seen even at doses significantly higher than sufficiently active doses. In such cases, decision criteria for stopping the escalation can be unclear. A related property of targeted therapeutics is (frequently) a limited ability to objectively determine the occurrence of dose-limiting adverse events (AE). A recent review (10) using data from 201 phase I trials reported that only about 30% of trials with non-cytotoxics reported objectively quantifiable or clinically gradable AEs (objectively quantifiable biologic anomalies include renal function, liver function, hematologic function, level of serum creatine phosphokinase, metabolic parameters, or ventricular dysfunction; clinically gradable AEs are gradable by the physician with some difficulty, such as skin reactions, mucositis, and diarrhea). The result of more subjective AEs (i.e., AEs that could not be objectively measured by the physician, such as pain, fatigue, and multiple combined side effects) is the additional ambiguity in DLT determination in


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early-stage clinical trials resulting also in ambiguity in MTD. This ambiguity can have significant impact on efficacy, as it has resulted in the use of less tolerable doses over longer duration when lower doses would suffice, thus causing poorer adherence and concomitant lower efficacy. A meta-analysis of 24 phase I trials of targeted agents at The University of Texas MD Anderson Cancer Center (Houston, TX) found that higher doses led to substantially higher numbers of dropouts due to toxicity with no concomitant improvement in clinical response (complete response, partial response, or stable disease) over doses that were roughly half of the MTD (11).

Because of these challenges and the changing regulatory landscape, a complementary strategy being used with increasing frequency is the identification of a biologically effective dose (BED) in phase I. The concept of BED has been discussed in oncology (12, 13), but its identification has been a challenge in practice due to narrow focus on pharmacodynamic markers. A broader set of "effect markers" can be used to guide identification of BED. An effect marker could be a pharmacodynamic, target engagement, or disease progression marker (e.g., change in tumor size for solid tumors or bone marrow blast count for some hematologic tumors). Related dose-finding strategies have also been considered previously (for example, see refs. 14–16).

Although the concept of BED has been reviewed (12), this is possibly the first discussion focusing on specific examples that demonstrate the clinical impact of effect markers. To motivate consideration of such examples, we first compiled a list of all approved oncolytic monotherapies and compared their approved dose(s) to MTD. Although the MTD- and effect marker–based strategies are complementary and can be used to determine appropriate and approvable dosing, neither strategy can ensure an optimal dose.

Data and specific examples below support improving dose selection strategies to benefit patients, providers, and the biopharmaceutical industry.

**Review of MTD versus Approved Dose**

The preliminary list of oncolytics for Fig. 1 was obtained from the NCI Dictionary of Cancer Terms (http://www.cancer.gov/publications/dictionaries/cancer-terms). A table of the key attributes of each oncolytic was constructed. (Supplementary Data S1). These attributes were MTD, maximum approved dose, minimum approved dose, and their respective sources. "Maximum" and "minimum" here refer to all indications for a given monotherapy. From the start of the search, combination therapies were excluded due to lack of adequate data. Data on compounds were obtained by manually searching Pharmapendium (17), an indexed, searchable database of regulatory preclinical, clinical, postrelease safety, and label data for approved compounds, Integrity (18), a database extracted from published literature and other sources, including Google (19); a Web search engine, Google Scholar (20); a specialized Web search engine that indexes scholarly literature; and RxList (21), an online medical resource providing prescribing information for U.S. prescription medications. The MTD-related contents were found by searching for each therapeutic agent and a set of key words (in combination or alone). Keywords included "MTD," "maximum," "maximal," "maximum tolerated dose," "tolerable," and "maximally tolerated dose." The MTD and highest administered dose values were extracted from texts found within either the "Clinical Pharmacology and Biopharmaceutics Review" or the "Medical/Clinical Review" sections of the FDA Approval Package for each therapeutic in Pharmapendium, or in primary literature found through Integrity, Google, and Google Scholar. The corresponding approved dose of each therapeutic was recorded from the "Dosage and Administration" section by searching for the generic name in RxList.com.

Of the 123 oncolytic monotherapies in the original list, 58 had well-defined MTD (i.e., a single, well-defined dose regimen had been identified as such in the literature). For an additional 19 compounds, no DLT was found at the maximum administered dose, so MTD was assumed to be equal to that maximum administered dose (a conservative estimate in terms of the analysis below, as the MTD is by definition higher than this). Therefore, MTD was available for 77 of the 123 oncolytic monotherapies. For the other 46, which include 7 monoclonal antibodies, the compounds (i) were developed without a record of an established MTD (typical of cytotoxins such as 5-fluorouracil, cytarabine, and oxaliplatin); (ii) had MTD found for one indication and approved dosing found only for another (e.g., bexarotene, for which early trials to determine MTD were run in patients with non-M3 acute myeloid leukemia, but the drug was approved for T-cell lymphoma), or (iii) had MTDs that were different for different indications [e.g., clofarabine, for which the MTD ranges from 2 mg/m² for solid tumors with a DLT of myelosuppression, to 40 mg/m² for acute leukemia with a DLT of hepatotoxicity (22)].

Figure 1 shows that roughly two-thirds of oncolytic monotherapies have approved doses less than MTD. These findings are consistent with a previous review, which found that, for about 30% of compounds, MTD is not within 20% of the approved dose (23). More details are available in Supplementary Data S2 and Supplementary Fig. S1.

**Examples of the Clinical Impact of Effect Marker–Based Dosing Approaches**

Figure 1 provides evidence that non-MTD development strategies have been successfully implemented, including strategies for a number of drugs with doses substantially less than MTD. The use of these strategies can be motivated, for example, by (i) the MTD being above a pragmatic dose for many new targeted therapies or (ii) safety considerations. Examples of how development can succeed without using MTD, such as through modeling and simulation-based methods, illustrate the impact of such strategies.

The nonexhaustive list of examples that follows includes both mAbs and small-molecule drugs. Examples were selected (from literature published between 2000 and 2013) by the degree of impact, broad applicability of strategy for that impact, diversity of methods and pipeline stages of impact, and ease of exposition. The examples are summarized in Table 1 and described briefly below.

**Monoclonal antibodies**

**Cetuximab (dose escalation stopped on the basis of target saturation)**. Cetuximab (marketed as Erbitux by Lilly) is an EGFR antagonist mAb approved in metastatic colorectal and head and neck cancer. In a phase I trial (cetuximab as single agent or with chemotherapeutics), patients received weekly doses escalating from 5 to 400 mg/m² i.v. (24). Cetuximab was well tolerated
Target engagement, instead of MTD, was used to support dose selection. In the absence of direct measurement of target engagement, clearance of cetuximab was used to infer target engagement. Pharmacokinetic data showed that the clearance of cetuximab decreased with increasing dose approaching a plateau at around 200 mg/m². This saturation is likely to occur when target receptor is maximally bound, implying maximal target engagement in circulation and tissues with drug accessibility. When cetuximab binds to EGFR, it gets eliminated by degradation mediated via EGFR internalization. This EGFR-mediated clearance is an example of target-mediated drug disposition (TMDD). The effect of TMDD on pharmacokinetics is typically observed at lower doses, as in this case. TMDD saturation (at higher doses) is a useful indirect measure of target engagement that only requires pharmacokinetic data. If signaling through EGFR enables tumor growth, maximal blocking of EGFR by an antagonist should result in maximal therapeutic effect. On the basis of TMDD saturation, a dose of 200 mg/m² weekly was recommended for phase II. Cetuximab was approved with a maintenance dose of 250 mg/m² weekly (with initial dose of 400 mg/m²).

Pembrolizumab (phase II dose selected using pharmacodynamics and tumor size marker). Pembrolizumab (marketed as Keytruda by Merck) was the first mAb approved in the United States targeting PDCD1 (PD-1) receptor. The dosing strategy for this novel immuno-oncology compound was driven by understanding of BED. First, an optimally designed, 13-patient, within-subject dose escalation study focused on elucidating the pharmacokinetics–pharmacodynamic relationship by measuring IL2 response over a 2,000-fold dose range of 0.005 to 10 mg/kg (25). The BED was estimated to be 2 mg/kg because IL2 stimulation approached saturation at exposures consistent with this dose. The BED of 2 mg/kg and maximum administered dose of 10 mg/kg were explored in later clinical studies. Early clinical response measured by change in tumor size from baseline was used to perform exposure–response analysis demonstrating similar anti-tumor response over the dose range from 2 to 10 mg/kg (26). In 2014, pembrolizumab was approved at a dose of 2 mg/kg every 3 weeks for treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

Small molecules

Idelalisib (phase II dose selected using pharmacodynamics and tumor size marker). Idelalisib (marketed as Zydelig by Gilead), a selective inhibitor of PI3Kδ, was approved by FDA for three types of blood cancers in 2014: non–Hodgkin lymphoma

Summary of results from the review of MTDs and approved doses. Roughly two thirds (48/77) of the compounds have approved doses less than MTD, with roughly one third of them being dosed at less than one half of MTD. Compounds are often approved for multiple indications, sometimes with different dosing for different indications. “Dose” here refers to the minimum approved dose (across indications). “Dose slightly below MTD” is for the cases in which the dose is greater than half MTD but still less than MTD: This is not always distinguishable from the other two cases because MTD is often only established to within a factor of two. Using the maximum approved dose (maximum across indications) gives similar results (available in Supplementary Fig. S5). Where MTD and approved doses have different schedules, average dose amount per week was used for the ratio (details available in Supplementary spreadsheet). Combination regimens (and compounds only approved as part of combinations) were excluded from all analyses. Also, four compounds with a dose greater than published MTD have been listed in Supplementary Data S2 along with potential explanations for how this situation could arise.

Table 1. MTD, effect marker–based dose, and clinical dose of selected drugs for which clinical development programs used effect markers

<table>
<thead>
<tr>
<th>Compound</th>
<th>MTD</th>
<th>Effect marker–based dose</th>
<th>Clinical dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab</td>
<td>Not reached</td>
<td>200 mg/m² q/w</td>
<td>250 mg/m² q/w as maintenance dose (initial dose = 400 mg/m²)</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Not reached up to 10 mg/kg q2w</td>
<td>2 mg/kg q3w</td>
<td>2 mg/kg q3w</td>
</tr>
<tr>
<td>Idelalisib</td>
<td>Not reached up to 350 mg twice a day</td>
<td>150 mg twice a day</td>
<td>150 mg twice a day</td>
</tr>
<tr>
<td>Decitabine</td>
<td>1,500–2,000/mg/m² over 1–3 days</td>
<td>15–20 mg/m²/d over 10 days</td>
<td>20 mg/m²/d over 5 days</td>
</tr>
<tr>
<td>Vismodegib</td>
<td>Not reached up to 540 mg/d</td>
<td>150 mg/d</td>
<td>150 mg/d</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>250 mg twice a day</td>
<td>250 mg twice a day; pharmacodynamic marker helped in target population selection</td>
<td>250 mg twice a day (ALK-positive patients)</td>
</tr>
<tr>
<td>Galunisertib</td>
<td>Not able to determine MTD due to potential cardiovascular DLT</td>
<td>160–360 mg/d with intermittent dosing (2 weeks on and 2 weeks off)</td>
<td>Not approved yet; pharmacokinetic–pharmacodynamic model-based intermittent dosing enabled clinical development</td>
</tr>
</tbody>
</table>

Abbreviations: q1w, every week; q2w, every 2 weeks; q3w, every 3 weeks.
(NHL), chronic lymphocytic leukemia (CLL), and follicular lymphoma. The phase I study explored a dose range of 50 to 350 mg along with twice-a-day and every-day schedules (27). No DLT was observed and hence no MTD was established in phase I. Instead of selecting the maximum administered dose as RP2D, two effect markers were used to inform RP2D, phospho-AKT(T308) inhibition (a pharmacodynamic marker) and tumor size change from baseline (28). Hyperactivation of the PI3K pathway in CLL cells, as indicated by elevated levels of phospho-AKT(T308), was present at baseline in the patients in the CLL cohort in the phase I study. After idelalisib treatment, Akt activation was reduced to levels similar to those in normal B cells at doses ≥100 mg twice a day. Considering interindividual variability in \( C_{\text{in}} \), modeling and simulation were used to choose the dose of 150 mg twice a day so that \( C_{\text{in}} > EC_{50} \) (measured for phospho-AKT(T308) inhibition) would be achieved for most CLL and NHL patients (5). Furthermore, tumor response, assessed by changes in tumor size, approached plateau in CLL and NHL patients at exposures obtained with a dose of 150 mg twice a day (5, 27, 28), adding strong evidence to justify dose selection. The BED of 150 mg twice daily, estimated using effect markers, is the approved dose of idelalisib.

Decitabine (approved dose is only 1% of MTD). Clinical trials of decitabine (marketed as Dacogen by Osuka), a DNA methyltransferase inhibitor, were initiated about 30 years ago (29). The phase I study focused on identifying MTD, which was determined to be 1,500 to 2,000 mg/m²/course. Phase II studies used high doses over 1 to 3 days, assuming higher doses would be more efficacious, and showed disappointing efficacy. About a decade ago, the drug was resurrected based on a better understanding of the mechanism of action. This time, the focus of clinical trials for acute myelogenous leukemia (AML) was on identifying a dose based on pharmacodynamics rather than an MTD (29). Gene expression–based pharmacodynamic markers of estrogen receptor (ESR1) and cyclin-dependent kinase inhibitor 2B (CDKN2B), genes frequently methylated in AML, were used in setting the dose (30). In these trials, 15 to 20 mg/m²/d for 10 days was associated with pharmacodynamic changes, a dose much smaller than MTD. The drug was approved by the European Medicines Agency (EMA) at a dose of 20 mg/m²/d (infused over 1 hour) for 5 days for AML in older adults, and by FDA for myelodysplasia at the same dose. While decitabine was rejected for geriatric AML by FDA, pharmacodynamic-based dosing enabled rational evaluation of the efficacy of decitabine in AML.

Vismodegib (phase II dose determined using pharmacodynamic marker in skin and pharmacokinetics). Vismodegib (marketed as Erivedge by Genentech), a sonic hedgehog pathway inhibitor, was approved by FDA for basal cell carcinoma in 2012. In phase I, three dose levels were administered (31): 150, 270, and 540 mg/d. No DLT was observed and hence no MTD was established in phase I. Unexpectedly, similar exposure was observed over 150 to 540 mg/d. Suppression of GLI1 expression in skin punch biopsies at all the doses helped to confirm that the drug caused pathway suppression even at the lowest dose tested. Although a full dose–response (pharmacokinetic–pharmacodynamic) relationship was not established, flat dose-response (over 150 to 540 mg/d) and evidence of pathway suppression in the clinic guided dose selection in the face of saturable pharmacokinetics (32). Finally, 150 mg/d was the recommended phase II dose and became the approved dose.

**Crizotinib (pharmacodynamic marker–enabled identification of target population).** Crizotinib (marketed as Xalkori by Pfizer), a dual c-Met (MET) and Alk tyrosine kinase (ALK) inhibitor, is a drug for which understanding the mechanism of action enabled patient selection. In an early phase I trial of patients with solid tumors refractory to standard-of-care treatment, two ALK-positive non–small cell lung cancer (NSCLC) patients showed response (33). Two patients would normally be too few to draw conclusions in the absence of other evidence. Data from murine models showed that inhibition of ALK (as a pharmacodynamic marker) correlated with tumor growth inhibition (TGI) while c-Met inhibition did not (34). On the basis of clinical tumor response and preclinical ALK inhibition data, a decision was made to run a phase I trial on ALK-positive NSCLC patients. Eighty-two patients were selected after ALK screening of 1,500 NSCLC patients. An overall response rate of 57% and an estimated probability of 6-month PFS of 72% were reported (33). These response rates would clearly have been much lower if measured across all 1,500 patients. While the chosen dose of 250 mg twice a day was also MTD, a mathematical model based on the preclinical data was used to support the hypothesis of sufficient ALK inhibition at that dose (35). Crizotinib received accelerated approval by FDA in 2011 at a dose of 250 mg twice a day.

**Galunisertib (pharmacokinetic-pharmacodynamic model–enabled dosing despite cardiovascular safety signals in preclinical species).** The TGF\(\beta\) receptor 1 kinase (TGFBR2) inhibitor galunisertib showed cardiovascular safety signals in preclinical species, an observation that can be expected for this mechanism. Preclinical observations of cardiovascular AEs indicated potential for cardiovascular-related DLT, meaning that MTD-based phase I was not a viable development path for this compound. A pharmacodynamic marker–based approach enabled continuation of the program without running an MTD-finding study. A preclinical pharmacokinetic–pharmacodynamic model predicted the therapeutic window (36). The model represented quantitative relationships among pharmacokinetics, phospho-SMAD2/3 inhibition (pharmacodynamics), and TGI. In preclinical data, an average of 30% pSmad inhibition over a 24-hour period achieved sufficient TGI (37). After updating the preclinical pharmacokinetic–pharmacodynamic model with human pharmacokinetic data, the desired phospho-SMAD2/3 inhibition was predicted to be achieved at doses of 80 to 150 mg twice a day. Furthermore, simulations of several dosing regimens showed that intermittent dosing was likely to be safe and efficacious. Galunisertib is being tested in a phase II/III clinical trial for myelodysplastic syndromes at 150 mg twice daily (trial registration ID: NCT02008318) and in a phase II clinical trial for hepatocellular carcinoma at 160- and 300-mg total daily doses administered intermittently with 2 weeks on followed by 2 weeks off (trial registration ID: NCT01246986).

**Discussion**

Dose selection is one of the most critical (as well as difficult) strategic decisions in clinical development, and no one-size-fits-all approach to dosing can be justified in the development of anticancer drugs. Both MTD- and effect marker–based dosing
have their roles. Historically, much more attention has been given to develop clinical study designs to identify MTD, as is evident from the variety of MTD-finding methods (3+3, CRM, TITE-CRM, accelerated titration, etc.). Strategies are needed now to guide optimal dose selection. A rational alternative to MTD-focused clinical study design may be to use effect marker data from pre-phase I and phase I/II to select (at least two) doses for a randomization, dose-ranging phase IB/II study (Fig. 2). Effect marker–based strategies provide a reasonable way to use all available data (including MTD or maximum administered dose) to inform those doses. These strategies have also been used successfully in concert with pharmacogenomics studies to support patient stratification (38). Phase II trials then evaluate efficacy and safety and find a dose with acceptable benefit/risk characteristics, starting not only with MTD, but with at least two doses guided by both the BED and the MTD. Clinical development of pembrolizumab is a clear example to exhibit such a dosing strategy in practice (with dose range of over 5-fold). It also shows that the proposed dosing strategy could be implemented even in a fast-moving program with approximately 3.5 years from first-in-human trial to approval.

Dose selection challenges such as nonquantifiable and/or unachievable MTD are increasingly common in oncology clinical trials. In some cases of targeted therapeutics, in particular mAbs, phase I trials may not even establish DLT, especially in short-duration early trials. For example, a high proportion of mAbs lack MTD (Supplementary Data S1). Selection of a higher dose increases the chances of toxicity in later, longer-duration duration trials. The resulting lower tolerability can even have a negative impact on efficacy due to toxicity-driven early discontinuation of dosing (or reduced dose/frequency; ref. 11). For mAbs, higher doses increase the cost of goods, potentially increasing the pricing and competition challenges in the market, as well as increasing the risk that future studies will show lower doses to be equally efficacious, and potentially putting patient access at risk. The utility of effect markers can also go beyond dose selection to patient selection (e.g., crizotinib) and, possibly, combination therapies (39). A suboptimal decision on dosing in early trials can prove to be a costly decision later and has even delayed patient access to effective drugs (29). Improving dose selection will benefit the patient, provider, and biopharmaceutical industry by improving health care and its economics.

Approaches based only on pharmacodynamics can be limiting as they require sufficient biologic understanding and evidence. Peripheral markers with such properties are not always available, nor are tumor biopsies for biochemical analysis. Therefore, we propose using a broader set of effect markers. For many mAbs, target engagement has been an important dose-driving marker. The use of tumor size can be an important effect marker for making decisions early in development, especially (and with more statistical power) when continuous tumor size reduction is used directly without discretization into the RECIST categories (40, 41). Sometimes toxicity, such as neutropenia, can also be a useful effect marker. For some targeted agents, mechanism-based AEs, such as skin rash can also be used (24).

Neither the MTD-based strategies nor the effect marker–based strategies are able to ensure an optimal dose. With the effect marker–based approaches, it is always possible that a lower dose (between approved dose and lower administered dose) is just as effective and safer, or that a higher dose would not have a higher
response rate with only marginally more risk. Similarly, the MTD approach could yield dosing with more risk than necessary and even compromise efficacy through lower tolerability, decreasing the ability to maintain recommended schedules (or adherence).

Proper dose selection in oncology should follow a multifactorial decision process leading to a randomized, dose-ranging study. At a recent FDA-AACR conference in 2015 (42), key opinion leaders from industry and FDA argued for increased quantitative analyses as critical components of development decision making. When they can be applied, model-based strategies allow decisions based on quantitative estimates of both benefit and risk. These strategies also allow industry to provide the necessary resources for research, and, typically, to more rapidly bring medicines to those who need them, thus motivating an increase in use of these development strategies. Such strategies would also reduce the risk of dosing optimization as a postmarketing requirement/commitment, and as a result benefit all the stakeholders of pharmaceutical discovery and development.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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