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ARE DOSES AND SCHEDULES OF SMALL MOLECULE TARGETED ANTICANCER DRUGS RECOMMENDED BY PHASE I STUDIES REALISTIC?

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Statement of 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.
Abstract
Tolerability of molecularly targeted agents (MTA) used in cancer therapeutics are 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 if 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 monoclonal antibody MTA (MA-MTA) approved by the FDA in the last twelve years. There was a significantly increased percentage of grade 3 or 4 adverse events reported with SM-MTA compared to MA-MTA (40% vs 27%, RR 1.5, 95% 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 2 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 vs 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.

Introduction
The latter half of the 20th century focussed 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 are often loosely termed as molecularly targeted agents (MTA). These agents have been developed to selectively affect the tumour or supporting vasculature and are thought to have a better therapeutic index compared to chemotherapy. MTAs can be monoclonal antibodies (MA-MTA) or chemical entities with molecular weights of
approximately 500 often called small molecules (SM-MTA). We reviewed ninety oncology products for one hundred and seventy eight indications granted approved by the U.S. Food and Drug Administration (FDA) during the last twelve 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 (PK) and pharmacodynamic (PD) profile of a new drug or drug combination. The R2PD is crucial as it 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 clinical relevant toxicities found in registration trials were previously described in early trials. This review included data studying molecularly targeted agents 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 molecular target agents 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. In order 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 R2PD derived from phase I trials.

Materials and Methods

Data Sources

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

Afterwards 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 in order 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. Paediatric anticancer drugs, drugs targeting DNA or microtubules directly and immune checkpoint modulating agents were excluded.

Two reviewers (DR and BJ) assessed publications involving these group of target agents, prioritizing phase 1 clinical trials, and phase 3 trials involved on their final approval. Other potential phase 2 or 3 studies could be also reviewed if they were considered as potentially relevant. Finally, the main conclusions were assessed also by a third reviewer (UB).

**Parameters assessed**

The present analysis studied dose interruptions and dose reductions in MTAs in phase III studies and compared this to the RP2D generated from phase I studies. All toxicities reported in phase I and phase III studies used National Cancer Institute common toxicity criteria adverse event (NCI-CTC-AE) reporting. We defined dose modification as a frequent occurrence (= or >30%) or not.

We also studied the phase I trials to see if PD studies were done at the R2PD and if a pharmacodynamically active range of dose levels were 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 $\chi^2$ 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 36 MTAs were included in our analysis. A total of 130 articles and
abstracts were assessed according to our predefined inclusion criteria in order to describe accurately each drug safety profile. Figure 1.

Eighty-six per cent of SM-MTA were developed in phase III trials with exactly the same dose and schedule that was defined as RP2D in early phase 1 trials.

There was a significantly increased percentage of grade 3 or 4 NCI CTC AEs reported with SM-MTA compared to MA-MTA (40% v 27%, RR 1.5, 95% 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. Further, a majority of MA-MTA were developed and finally approved in combination with classic chemotherapy 69% (18/26) and tolerance of antibody-chemotherapy combinations was not significantly different compared to chemotherapy alone; grade 3-4 toxicity reported as a single agent and in combination was 61% v 68% respectively, (RR 1.10, 95% CI 0.89-1.81 p=0.37).

In contrast, of all FDA registered SM-MTA 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%. Importantly 64% (18/28) of SM-MTA had equal or more than 30% of patients requiring dose adjustments, and up to 25% (7/28) of them presented more than 60% of patients requiring dose modifications. However, only 9% of patients finally required a dose discontinuation due to drug related toxicity. Figure 2 and 3.

In contrast with targeted antibodies, only 5/50 (12%) of SM-MTA were approved in combination with classic chemotherapy, hormone therapy or other MTA’s. There was a statistically significant increased rate of grade 3-4 toxicities described for combination trials involving SM-MTA compared to 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% v 46% and 8% vs 15%, RR 1.0 95% CI 0.7-1.4 p=0.89 and 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 described dose interruptions and reductions related to the study drug. Table1 Supplementary.

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 based on PK and PD data and had a RP2D lower than the MTD, had a significantly reduced percentage of dose modifications compared to those trials where the RP2D and MTD were the same. (32% vs 50%, RR: 0.64 IC95% 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 patients quality of life. Several publications have discussed concordance of toxicity in early and late clinical trials of MTAs (7-10). Jardim et al. in a recent publication concluded that early trials could accurately predict a safety profile of new cancer drugs. Focusing in 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 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 findings focussed 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 1 trials with new MTA required significant reductions in dose intensity at any time during their treatment. Therefore they proposed a new modification of the classical definition of MTD, suggesting that recommended phase 2-dose assessment should incorporate all available information from any cycle including less severe toxicities (such as grade 1-2 toxicities) leading to dose modifications (7-9). We would 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 present manuscript we could only find the timing of dose reductions/interruptions in 1 out 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 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 other them, 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 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 non-tolerable. Figure 4.

This is of particular relevance to MTAs in combination studies. Recently, as an example of combinations toxicity, Rugo et al reported the incidence and time course of everolimus related events in Bolero-2 trial. Remarkably, 62% of patients treated in everolimus arm required of 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 PK and PD data benchmarked to preclinical models and toxicity past the 1st 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 if the lower dose is within a pharmacodynamically active range as lowering the dose below that could lead to loss of activity. This is 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 to its maximal pharmacodynamics potential. (49) It is crucial that phase I studies report pharmacodynamically active ranges rather than pharmacodynamics 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 patients and healthcare providers alike.
LEGENDS

Figure 1. Molecular targeted agents 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%.

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.

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

Table 1. Supplementary data. Detailed description of dose and schedule developed and toxicity reported in phase I and registration trials for each SM-MTA.


Figure 1

90 ONCOLOGY DRUGS RECEIVED FDA APPROVAL FROM JAN 2002 TO FEB 2015

34 MOLECULAR TARGET AGENTS APPROVED

28 SMALL MOLECULES
- AXITINIB
- PAZOPANIB
- SUNITINIB
- VEMURAFENIB
- DABRAFENIB
- TRAMETANIB
- EVEROLIMUS
- TEMSIROLIMUS
- REGORAFENIB
- VANDEDATINIB
- CABOZANTINIB
- SORAFENIB
- IMATINIB
- NILOTINIB
- DASATINIB
- PONATINIB
- BOSUTINIB
- LAPATINIB
- ERLOTINIB
- GEFITINIB
- CRIZOTINIB
- CETIRINIB
- VISDEMOGIB
- IDELASINIB
- LENVATINIB
- IBRUTINIB
- RUXOLITINIB
- PALBOCICLIB

6 TARGET ANTIBODIES
- CETUXIMAB
- BEVACIZUMAB
- TRASTUZUMAB
- PANITUMUMAB
- PERTUZUMAB
- RAMURACENIB

* N=28
PHASE 1 TRIALS

** N=50
REGISTRATION TRIALS: PHASE II AND III
Figure 3

DOSE REDUCTIONS (%)

AXITINIB  PAZOPANIB  VEMURafenib  DABrafenib  TRAMETanib  EVEROLIMUS  DISPLEROSIMUS  SUNITINIB  SORAFENIB  BOZANTINIB  IMATINIB  Nilotinib  DASATINIB  PONATINIB  BOSUTINIB  LAPATINIB  ERLOTINIB  GEFTINIB  CRIZOTINIB  CETIRINIB  IPSDEMOGIB  IDELASINIB  LENVATINIB  IBRUTINIB  NUXOLTINIB  PALBOCICLIB
**Figure 4**

**ESCALATION COHORT**

**MTD selection:**
- Minimum PD effective dose
- Maximum tolerable dose

**RECOMMENDED DOSE RANGE**

**EXPANSION COHORT**

To confirm **RP2D** if:
- Tolerable in 12-20 patients.
- Long observation (2 cycles) should be completed.
- Dose modifications in less than 30% of patients
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