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Review

Clinical efficacy of the optimal biological dose in early-phase trials of anti-cancer targeted therapies

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Abstract ***Background:*** Determining the optimal biological dose (OBD) has been described as an alternative strategy to the maximum tolerated doses (MTDs) for identifying the recommended phase II trial doses (RP2Ds) of phase I anti-cancer therapies. However, the clinical relevance is still unknown. An extensive review was performed to assess if the OBDs defined in early-phase trials were useful for subsequent drug development and approvals.
Methods: All the molecular targeted therapies approved by the Food and Drug Administration (FDA) in solid oncology or in haematological malignancies before July 2018 were listed through the National Cancer Institute Database. The early-phase trial publications investigating these drugs as single agents were retrieved and analysed to identify the drugs for which OBDs were reported. The publications of subsequent pivotal efficacy clinical trials leading to the approvals were retrieved, and OBDs compared with the final labelled doses and dosing schedules.
Results: A total of 87 early-phase trial publications were analysed, corresponding to 81 FDA-approved targeted therapies. OBDs were reported for 40% (32/81) of these drugs (19 small molecules, 13 monoclonal antibodies). MTDs were not identified for 59% (19/32) of molecules. When the OBDs were selected as the RP2Ds (18/32 molecules), the final FDA-approved doses

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were consistent with the OBDs for 83% of the drugs, which is much higher than the previously reported 58% rate when MTDs were chosen as the RP2Ds.
Conclusion: Although still poorly investigated, the OBD may be a relevant and complementary end-point for early-phase trials of targeted therapies.

1. Introduction

Since the early 2000s, many molecular targeted therapies have been approved in haematology and solid oncology, including small molecules or monoclonal antibodies (mAbs). New questions were raised about the optimal strategy for defining the best doses and dosing schedules. Indeed, the approach traditionally implemented for conventional chemotherapy agents relies on dose-escalation trials meant to identify the maximal tolerated doses (MTDs) and the recommended phase II trial doses (RP2Ds). However, this strategy may not be adequate for novel targeted drugs, for which the dose-efficacy and dose-toxicity curves may not be correlated [1–3], and efficacy may occur at doses that do not induce clinically significant toxicity [4].

As a consequence, novel drug development strategies meant to identify the best doses and dosing schedules of novel targeted agents have been proposed [5,6]. Among them, determination of the 'optimal biological dose' (OBD), also called 'biologically effective dose' appears promising [7]. Indeed, identification of the minimal dose associated with an optimal predefined biological effect, through measurement of target inhibition and pharmacokinetics analyses, might be a good complementary approach for defining the RP2Ds of targeted therapies [4,7]. However, there are no data about the actual relevance of this end-point, in terms of clinical efficacy. The present review study aimed at assessing the clinical relevance of OBDs, defined during early-phase trials, for further approvals.

2. Materials and methods

2.1. Study design

This systematic review study was conducted in three consecutive steps.

1) Identification of the Food and Drug Administration (FDA)–approved targeted agents, for which early-phase trials defined OBDs:

All the molecular targeted therapies approved before July 2018 by the FDA for haematological or solid malignancies were collected through the National Cancer Institute Database (https://www.cancer.gov/about-cancer/treatment/drugs). The compilation of all early-phase trial publications was performed using MEDLINE via PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) and using the American Society of Clinical Oncology (ASCO) website, with the search terms 'compound name' or 'compound code', 'phase I' and 'early phase trial'. Identifications of OBDs, doses/dosing schedules and biological effects were tracked in the article bodies. OBD was defined as the lowest dose shown to inhibit a drug target reliably or to achieve a target plasma concentration [8] and was reported as the biologically effective dose by authors. The following elements were collected for all considered drugs: name of the first author; date of publication; studied tumour types; maximum tolerated dose if any; RP2D if any; reported OBD; OBD-related biological effects; OBD as the primary end-point of the trial (yes *vs* no) and structure of the drug (small molecules, or mAbs).

Early-phase trials investigating more than one investigational molecular targeted agents or those focussing on specific populations or ethnicities were excluded, as were those involving active immunotherapies, such as vaccines or chimeric antigen receptor T cell (CAR T cell) therapies, because of their specific and complex mechanisms of action.

2) Identification of the clinically effective doses in subsequent pivotal efficacy trials leading to FDA approvals:

We identified the subsequent efficacy clinical trials leading to the first FDA approvals and the dose/dosing schedules that had been tested, through the 'clinical studies' section of the structured product labelling (SPL) document of every compound, using the website https://nctr-crs.fda.gov/fdalabel/ui/search. The corresponding publications were then retrieved using the following keywords on PubMed: 'compound name' or 'code' and 'phase III trial' ('phase II trial' or 'phase I trial' when appropriate). The following elements were collected for every selected article: name of the first author; date of publication; studied tumour types; dose and dosing schedule tested and estimated value of the treatment effect on the primary end-point. Moreover, the following data were collected in the first FDA approvals: approval year; type of approval (accelerated or full), labelled dose/dosing

schedules and tumour indications, using the website https://www.accessdata.fda.gov/scripts/cder/daf/.

3) Comparison of OBDs and clinically effective doses:

The consistency in between the OBDs reported in the early-phase trials, the clinically effective doses reported in efficacy trials leading to FDA approval and the FDA-labelled doses/dosing schedules were finally assessed for each selected drug.

The data extraction was performed by two authors (P.C. and M.E.-M.). They were verified by all coauthors.

2.2. Statistical analysis

All analyses were descriptive. Qualitative data were described by percentages.

3. Results

As of July 2018, a total of 83 molecular targeted therapies were approved by the FDA for haematological or solid malignancies. Two of them were excluded because they were active T-cell immunotherapies. For the remaining 81 therapies, 87 early-phase trials were identified (Fig. 1). The concept of OBD was mentioned in the early-phase trials of 50 of 81 of these FDA-approved molecules (62%). Actual OBDs were reported in 32 early-phase trials, corresponding to 32 molecular targeted therapies (40%) (Appendix). One trial was a pilot biological study of lapatinib, while all others were phase I trials. All assessed trials were published between 1999 and 2017. The median year of publication was 2010. As shown in Table 1, 19 of 32 were small molecules (59%), while 13 of 32 were mAbs (41%). OBD identifications were clearly reported as the primary objectives of the early-phase trials for 7 drugs (22%). The clinical studies that led to the first FDA approvals of small molecules were phase III efficacy trials for 12 of 19 of them (63%) and phase II trials for 7 of 19 of them (37%). For mAbs, these were phase III trials for 10 of 13 (77%), phase II trials for 2 of 13 (15%) and phase I trial (cohort expansion) for 1 of 13 (8%).

For 19 of the 32 studied agents (59%), no MTDs were found during the early-phase trials despite dose escalations, including 9 small molecules and 10 mAbs and corresponding to 47% and 77% of all tested small molecules and mAbs, respectively. Among the 13 drugs with reported MTDs, the OBDs were lower than the MTDs for 10 of them (77%) and similar for 3 of them (23%).

For 18 of 32 drugs (56%), the OBDs were chosen as the RP2Ds, including 10 small molecules (corresponding to 53% of all small molecules) and 8 mAbs (corresponding to 62% of all mAbs). Of note, no MTD had been found for most of these drugs (11/18, 61%, including 5 small molecules and 6 mAbs). The 14 remaining drugs, for which RP2Ds were not the OBDs (44%), comprised 9 small molecules and 5 mAbs. These RP2Ds were superior to the reported OBDs for 13 of 14 of these drugs (93%), cetuximab being the only exception. Among these 14 drugs, MTD had been found for 6 of them, of which 5 were chosen as RP2Ds (36% of drugs for which OBDs were not chosen as RP2Ds). For the 9 remaining drugs (64%), the rationale sustaining the RP2D selection was not clearly reported.

Regarding FDA approvals, the labelled doses were similar to the OBDs for 19 of the 32 drugs with reported OBDs (59%), corresponding to 47% of small molecules

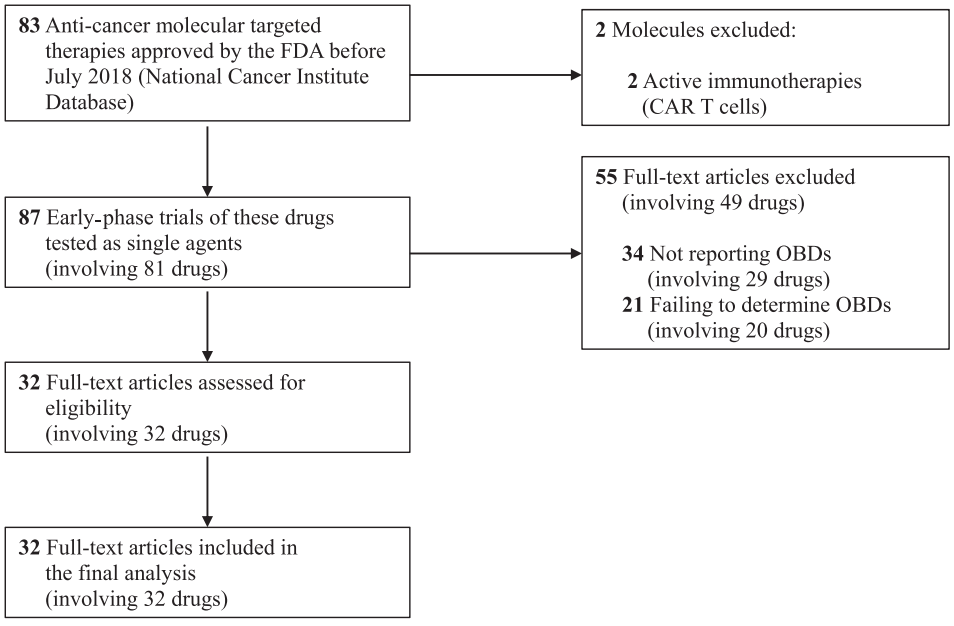

Fig. 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) diagram detailing article selection. CAR T cells, chimeric antigen receptor T cells; FDA, Food and Drug Administration; OBDs, optimal biological doses.

Table 1
Characteristics of the considered drugs and associated trials.

MTD reached in early-phase trials	Yes	13/32 (41%)	Small molecules	10/13 (77%)
			mAbs	3/13 (23%)
	No	19/32 (59%)	Small molecules	9/19 (47%)
			mAbs	10/19 (53%)
OBDs selected as RP2Ds	Yes	18/32 (56%)	Small molecules	10/18 (56%)
			mAbs	8/18 (44%)
			MTD reached	7/18 (39%)
			Molecules granted under accelerated approvals	4/18 (22%)
	No	14/32 (44%)	Small molecules	9/14 (64%)
			mAbs	5/14 (36%)
			MTD reached	6/14 (43%)
			Molecules granted under accelerated approvals	7/14 (50%)
OBDs, FDA-approved doses	Yes	19/32 (59%)	Small molecules	9/19 (47%)
			mAbs	10/19 (53%)
			Molecules granted under accelerated approvals	5/19 (26%)
OBD selected as RP2Ds and FDA-approved doses	Yes	15/18 (83%)	Small molecules	8/15 (53%)
			mAbs	7/15 (47%)
			Molecules granted under accelerated approvals	4/15 (27%)

Abbreviations: MTD, maximum tolerated dose; OBD, optimal biological dose; FDA, Food and Drug Administration; RP2D, recommended phase II trial dose; mAbs, monoclonal antibodies.

and 77% of mAbs. Regarding the 18 molecules for which OBDs were chosen as the RP2Ds, the final FDA-labelled doses were consistent with the OBDs for 15 of them (83%), including 8 of 10 small molecules (80%) and 7 of 8 mAbs (88%). The three remaining molecules approved at doses different from OBDs were lapatinib, midostaurin and siltuximab. Their labelled doses were lower than the reported OBDs and than their RP2Ds. Two of them (lapatinib and midostaurin) were actually approved in combination with chemotherapy at lower doses. Siltuximab was approved at 11 mg/kg every three weeks, instead of 12 mg/kg every three weeks, which was the OBD and defined as the RP2D.

Interestingly, 4 drugs for which RP2Ds were not similar to the OBDs were finally approved at the OBDs: abemaciclib, cetuximab, obinutuzumab and necitumumab. Cetuximab was approved at intravenous 400 mg/m^2 loading dose followed by weekly 250 mg/m^2, although the reported RP2D was intravenous weekly 200 mg/m^2. Abemaciclib was approved at 150 mg orally twice a day, which is inferior to the MTD RP2D, which was set up at 250 mg orally twice a day. As for obinutuzumab and necitumumab, the approved dosing schedules were adjusted for chemotherapy combinations at doses that were similar to OBDs.

Overall, 19 of 81 (23%) assessed molecular targeted therapies approved by the FDA were approved at their OBDs.

The impact of the type of approval (accelerated versus full) on the results were explored. The FDA granted accelerated approval to 11 of 32 (34%) molecules, including 6 small molecules and 5 mAbs. OBDs were selected as the RP2Ds for 4 of them (36%), and the approved doses were similar to the OBDs for 5 of them (45%). When OBDs were chosen as the RP2Ds, the accelerated FDA-approved doses were consistent with the OBDs for all of them (100%), against 11 of 14 (79%) for the drugs that were directly fully approved.

Regarding the biological effects of small molecules, OBDs mainly relied on indirect effects on elements of the involved signalling pathways (11/19, 58%). For example, OBDs of imatinib and ponatinib, two breakpoint cluster region-Abelson tyrosine kinase (BCR-ABL) inhibitors, were based on the inhibitions of CT10 regulator-like (CRKL) protein phosphorylation, a substrate of BCR-ABL. Otherwise, the biological effects relied on direct inhibition of the target (6/19, 32%) (i.e. diminution of the formation of poly (ADP ribose) [PAR] for olaparib, a poly (ADP-ribose) polymerase [PARP] inhibitor), or receptor occupancy (2/19, 10%). For mAbs, the assessed biological effects involved receptor occupancy (6/13, 46%), followed by direct inhibition of the target activity (4/13, 31%), or indirect effects on components of the signalling pathways (2/13, 15%), and finally on target concentration associated

Table 2
Biological effects selected for the determination of the optimal biological doses.

Type of targeted therapy	Direct target inhibition	Indirect target inhibition	Target receptor occupancy or saturation	Target concentration of the drug associated with biological effects based on pharmacokinetic studies
Small molecules (n = 19)	6/19 (32%)	11/19 (58%)	2/19 (10%)	0/10 (0%)
mAbs (n = 13)	4/13 (31%)	2/13 (15%)	6/13 (46%)	1/13 (8%)

Abbreviations: mAbs, monoclonal antibodies; OBD, optimal biological dose.

with biological effects based on pharmacokinetic study outcomes (1/13, 8%) (Table 2).

Of note, in the early-phase trials of 18 other drugs, representing 22% of all approved targeted molecular therapies, no OBDs were finally reported although the concept of OBD was mentioned in the articles. Most of time, the authors failed to determine the OBDs because of the lack of correlation between drug doses and the assessed biological effects [9–26].

The time intervals from the publications of early-phase trials reporting OBD to the first FDA approvals were relatively short (median, 1 year; range, less than one year to 16 years for midostaurin), with no differences in between small molecules and mAbs.

4. Discussion

In 2014, Jardim *et al.* [27] showed that the RP2Ds had been used as the labelled doses for 97% of cytotoxic chemotherapy agents, against 58% of targeted agents approved in between 1990 and 2011, thereby suggesting the limitations of traditional toxicity-based trials for defining the optimal clinically effective doses of these novel drugs.

The first reason relates to the lack of direct dose-toxicity relationships for many of these drugs. In a review study of 201 phase I trials, dose-limiting toxicities were less frequently identified with targeted therapies (48%) than with cytotoxic drugs (89%) [28]. Consistently, in a review of 82 articles about mAb phase I trials, MTDs had been found in 16% of early-phase trials only [29]. In the present study, MTDs were reported for 53% and 23% of assessed small molecules and mAbs, respectively, corroborating these data.

The second reason is the frequent lack of direct dose-efficacy relationships, meaning that the highest tolerable doses are not necessarily the most effective doses, contrarily to what is accepted with most of cytotoxic chemotherapy agents.

To solve this issue, identification of the optimal biologically effective dose is frequently described as a relevant approach [1]. Indeed, the knowledge of the mechanisms of actions of these new targeted agents offers the opportunity to assess the biological effect magnitude induced by the novel drugs and thus to define the lowest dose associated with the expected pharmacodynamic effects. It was reported that OBDs were indeed frequently identified at lower doses than MTDs, thereby suggesting that this strategy could potentially reduce the toxicity profiles and the costs of anti-cancer treatments [7].

The present study first suggests that OBDs are still rarely assessed, reported in less than 40% of early-phase trials of recent FDA-approved targeted agents. When reported, they were chosen as the RP2Ds in 56% of cases. Our work suggests that the search for OBDs may be a relevant strategy, as 83% of the final approved doses were consistent with the OBDs, when they were selected as the RP2Ds. This percentage is much higher than the previously reported 58% with MTDs [27]. Moreover, when both MTDs and OBDs had been defined, the OBDs were lower for most of the studied agents (77%), hence corroborating the assumption that the OBD identification strategy could improve the safety of anti-cancer treatments. Niraparib, a recently approved PARP inhibitor, is an illustrative example. The MTD at 300 mg/day was defined as the RP2D, although the lower 80 mg/day dose was identified as the minimum biologically effective dose, based on PARP inhibition effects in peripheral blood mononuclear cells [30]. In 2017, niraparib was approved as a maintenance treatment for recurrent epithelial ovarian cancer at the MTD (300 mg/day), based on the positive NOVA trial outcomes [31]. However, this dose has subsequently been recognised as too high and toxic, and dose reductions based on patient weight and platelet count are now advised for prescriptions of niraparib in most patients and for on-going clinical trials [32,33].

Although these data about the clinical efficacy of OBDs are encouraging, they also raise issues. The selection and measurement of the adequate biological effects required for OBD identification are not easy, especially for mAbs [7]. We noticed that the measured biological effects associated with OBDs were heterogeneous among small molecules and mAbs, but also among some molecules of the same classes. For example, the OBDs of pembrolizumab and nivolumab, two programmed cell death protein 1 (PD-1) inhibitors, relied on interleukin (IL)-2 stimulation, and on PD-L1 occupancy, respectively [34,35]. The lack of validated biomarkers and thresholds for novel study agents contributes to this inconsistency. Such a complexity may explain why OBDs frequently rely on indirect effects on the involved signalling pathway components for small molecules and on receptor occupancy or saturation for most mAbs, as already reported [29]. It may also explain why actual OBDs could not be found for about a quarter of drugs, despite the mention of biological effective dose in the articles. For example, the authors demonstrated some pharmacodynamic effect-dose relationships as proofs of concepts and set up the RP2Ds of bortezomib [9], sonidegib [10] and vorinostat [11], based on other criteria, without defining OBDs. This observation is consistent with that of Sweis *et al.* [36] who reported that despite their increased uses, the impact of biopsy-derived pharmacodynamic biomarkers in phase I oncology studies remains uncertain on subsequent drug development, as no effects on subsequent dose or schedule were demonstrated. Another difficulty relates to the impact of the trial designs on the relevance of identified OBDs. For example, the number of assessed dose levels restricts the search in a dose window, as illustrated by nilotinib for which only two doses

were evaluated [37]. Of note, the rationale sustaining the selection of the RP2Ds was not clear in more than 60% of drugs, for which the RP2Ds were not based on OBDs or MTDs.

The present study has several limitations that are important to notice. First, we chose to restrain our analysis to single-agent studies for avoiding the effects of pharmacodynamic interactions. In addition, we assumed that approved doses were clinically effective, but this is debatable. Although clinical efficacy cannot be reduced to drug approvals, the FDA-labelled dose appeared as the most objective and assessable end-point for the present analysis. In particular, our research did not focus on unpublished early-phase trials for feasibility reasons, which did not allow us to assess the number of negative efficacy trials testing the OBDs, thereby leading to drug abandons before approvals.

5. Conclusions

Although being insufficiently investigated, OBD may be a relevant and complementary end-point to toxicity end-points traditionally assessed in oncologic phase I trials. Indeed the reported OBDs were found to be consistent with subsequent doses approved by the FDA for the large majority of oncology- and haematology-targeted therapies, when developed at these doses. The design of future early-phase trials should be adjusted to integrate systematic assessment of the biological effective dose, as a way of reducing the high attrition rate and costs in oncology drug development and improving the quality of life of patients.

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Conflict of interest statement

The authors have declared no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.08.002.

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