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Editorial Comment

Phase 1 trials of molecular targeted therapies: Are we evaluating toxicities properly?

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Over the last few years, oncology drug development has experienced a significant shift from traditional cytotoxic therapies to novel molecular targeted agents (MTA). One current burning challenge is to adapt drug development principles that have been set up nearly 50 years ago for cytotoxics to these novel therapies. In particular, it is now widely agreed that the spectrum of toxicity of these agents profoundly differs from the one observed with conventional chemotherapy.[1] Moreover, most of these agents are likely to be administered in a chronic fashion rather than for a pre-determined number of cycles. As the key aim of Phase 1 trials is to investigate toxicity and determine a recommended Phase 2 dose to be utilised in subsequent trials, the methodology, design and conduct of Phase 1 trials with MTA should probably be revised accordingly.

In this context, the classical definition of Dose-Limiting Toxicity (DLT) and Maximum Tolerated Dose (MTD) may not allow optimal documentation of toxicities displayed by these novel agents. As an example, the recommended phase 2 dose of dasatinib (70 mg bid) had to be re-evaluated and decreased to 100 mg qd at a later stage of its clinical development, mainly because of a high incidence of myelosuppression. Regarding the reasons to explain the high attrition rate of oncology drugs, nobody can tell in which proportion toxicity not captured in Phase 1 trials has led to drug development interruption.

A central issue to be addressed is that most of the MTAs are designed to be administered for a long period of time: therefore, delayed or cumulative toxicities would logically deserve more attention. However, these latter are currently not taken into account in the DLT definition. Three different types of 'late' toxicities could be identified: (1) late severe toxicities, i.e. G3+ toxicities occurring after the 1st cycle: these toxicities are commonly responsible for temporary treatment interruption or dose reduction according to the Phase 1 protocol; (2) prolonged or repeated 'moderate' (Grade2): although deemed to be tolerable, some moderate toxicities, such as rash or diarrhoea, significantly impact on patient's quality of life when becoming chronic, acquiring an 'intolerable' character; (3) cumulative toxicities: due to prolonged exposure to the drug, these toxicities require a specific management in order to remain tolerable and reversible. If all G3+ toxicities are reported in Phase 1 publications, their cycle of occurrence is rarely identifiable. Similarly, G2 toxicities are inconstantly and barely described. Several other pitfalls make late toxicities difficult to evaluate in phase 1 trials: the small number of patients included in Phase 1 trials (and the fact that only 50% of them remain on study after cycle 2), the highly-selected phase 1 population – which may not be representative of the all-coming oncology patients, and the treatment interruptions or dose-reductions authorised by protocol after cycle 1 that may mask potential late toxicities.

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This being said, can we reasonably expect grasping any clue about late toxicities from Phase 1 data? Postel-Vinay et al.[2] recently retrospectively evaluated 445 patients included in 36 phase 1 trials of molecularly targeted agents: the analysis of all G3+ events revealed that more than half of the severe toxicities were occurring after cycle 1, with no severe toxicities observed after cycle 6. Looking at all toxic events of renal, cutaneous and digestive type, the authors found that only 40% of the patients were presenting their most severe toxicity at cycle 1 and that the risk for presenting G2 toxicity was 28% between cycles 1 and 3 and 14% between cycles 4 and 6. Surprisingly, no cumulative toxicities were detected for these three toxicity types – probably mainly due to lack of power. When looking at the influence of the administration route, they found that the median number of toxicities per patient was five for oral drugs and only two for intravenous drugs; moreover, the risk of developing G3+ toxicity was almost three times higher with oral drugs. Interestingly, treatment management was different according to the route of administration of the drug: dose modifications and treatment interruptions occurred in, respectively, 10% and 14% of the cycles for oral drugs, versus only 4% and 5% of the cycles for intravenous drugs.

These results raise an important question: in the era of targeted therapies which are due to be administered in a chronic fashion, is cycle 1 sufficient to properly evaluate Dose Limiting Toxicities? Should we lengthen the DLT period or only focus on optimising management of these late toxicities through close collaboration with organ specialists? Having the knowledge of acute and severe toxicities of a new drug is absolutely essential and we shouldn't, therefore, discard the current DLT definition. Therefore, the authors of this work suggested introducing the concept of 'chronic DLT' on top of the current 'acute DLT' based on severe toxicity data from the 1st cycle only. Chronic DLT would, for example, encompass all G3-4 and intolerable or repeated G2 toxicities occurring between cycle 2 and 6, each event being weighted differently according to its cycle of occurrence (e.g. coefficient 0.5 and 0.33 for cycles 2–3 and 4–6, respectively). A chronic DLT would be defined when the weighted sum of events would reach 1. In case the dose defined using the 'chronic DLT' concept would be significantly different from the 'acute DLT', the toxicity and efficacy profiles of these two doses could be further evaluated in the expansion cohort of the Phase 1 trial or in a randomised Phase 2 trial, similarly to what had been done for example for temsirolimus.[3]

Although this concept is appealing, several hurdles still have to be crossed before it can be applied in the clinical setting. Firstly, there is currently no formal study demonstrating the negative impact of prolonged moderate toxicities on patient's quality of life; even if everyone recognises that a chronic G2 rash or diarrhoea – such as those caused by EGFR inhibitors – is intolerable for many patients and responsible for dose reductions or treatment interruptions, such study is warranted. Secondly, the determination of the coefficients that would be used to weight the toxic events should ideally be first done retrospectively through re-analysis of all toxicity data from a large number of Phase 1 trials; as most of the trials are multi-centric and funded by the industry, a prerequisite to have access to such data would be the collaboration of pharmaceutical companies. Thirdly, all toxicity types may not be relevant for this chronic DLT definition: the determination of which items should be included would require data based on patients' quality of life self-questionnaires as well as the advice of a group of experts, similarly to what had been previously done for establishing and revisiting the current DLT definition.[4] And last but not least, the cost and time required for analysing all these extra-data should ideally not prolong unreasonably the duration of Phase 1 trials and delay further drug development.

The second key issue to be dealt with is whether definition of DLT should be standardised or not. While guidelines have been established for the use of endpoints in Phase 2/3 cancer clinical trials, there is to date no consensus on what events should be considered DLTs in Phase 1 cancer clinical trials. Le Tourneau et al.,[5] in this current issue of EJC, retrospectively evaluated how DLTs were defined in Phase 1 trials of molecular targeted agents administered as single agents published over the last decade. Although the definition of DLT was almost always provided in the 155 Phase 1 trials, the definitions used were heterogeneous. For haematological toxicities, definitions almost always incorporated severity (grade 3/4 in 89%) and, less frequently, duration (15%). While severity was also important for non-haematological toxicities, most definitions aimed to identify moderate toxicities (72% required grade 2/3) rather than severe ones (5% required grade 4). To be considered DLTs, grade 2 non-haematological toxicities often assessed other criteria such as reversibility (50%) and duration (28%). Treatment delays or reduced dose-intensity were less commonly incorporated into definitions. Other significant observations were that DLT definitions varied significantly with administration schedule, grade 2 non-haematological toxicity being more often considered as a DLT in trials evaluating agents with a (near)-continuous schedule than in trials evaluating agents with an intermittent dosing. Finally, 25% of trials reported discordance between initial and final definitions of DLT.

The high degree of heterogeneity in DLT definitions is likely an appropriate reflection of differences in molecular targeted agents being tested in such schedule of administration. However, differences in the definitions of DLT across trials may render accurate comparisons between drug developments awkward. Where appropriate, the authors suggest the inclusion of the following may improve reproducibility and interpretation across trials: (1) specification of the DLT assessment period, (2) absolute severity according to NCI CTCAE classification as well as severity relative to baseline status, (3) minimum duration of toxicity, (4) reversibility of toxicity within a certain period of time and (5) necessity to delay treatment or to reduce dose-intensity.

In summary, oncology early drug development is currently facing exciting challenges about redefining drug development methods. The definition of novel approaches to optimally evaluate toxicity for monotherapy targeted therapies in the setting of Phase 1 requires first a retrospective analysis of what has been done so far, in order to build a new drug development model that would be validated prospectively in a second time. These are the foundations of a new EORTC initiative (within its New Drug Advisory Committee), named 'the Phase 1 methodology task-force', that aims at bringing together

high-level expertise from several Phase 1 centres as well as partnering with pharmaceutical industry to have access to the appropriate amount of Phase 1 data, in order to suggest new recommendations for toxicity evaluation, as well as DLT and recommended Phase 2 dose definitions in Phase 1 trials testing MTA as single agents.

Conflict of interest statement

None declared.

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