Learning from toxicity patterns in phase I trials during the era of mechanism targeted agents

In this month’s journal are companion papers describing observed toxicity in patients entering on phase I trials within the Royal Marsden Hospital (RMH), UK, and the MD Anderson Cancer Centre, USA (two of the biggest drug development units in the world) [1, 2]. These studies assessed patients enrolled in the period of 2005–2009 where oncology drug development has concentrated on molecular targeted agents (MTAs). What lessons can we learn from these studies to help us improve the care of patients on phase I studies?

A major ethical issue encountered while discussing entry to phase I trials is the risk of exposing patients to toxicity, when historical response rates to therapies in phase I studies are low [3–5]. Identification of patients who are at greater risk of toxicity or have less chance of response is important to enable informed discussion with a patient about the risk: benefit ratio of entering on a phase I study. Physicians often informally try to assess the risk of a patient going on to suffer from unacceptable toxicity before entry on a phase I study, but the criteria they use vary and have little or no evidence base [6].

The two studies reported here retrospectively analyse toxicity rates and risk factors in populations treated on phase I studies. There are minor differences between the studies; in particular, Molife et al. [1] from the Royal Marsden excluded patients receiving conventional cytotoxics from their analysis, while Wheler et al. [2] from the MD Anderson included patients who received cytotoxic (379 of 1181 patients in their cohort, of which 215 patients received a cytotoxic in combination with a targeted agent). However, both series reported similar grade 3 and 4 toxicity rates of 16% and 10.3%, respectively, with a possible drug-related death rate of 0.4% in both studies [1, 2].

There is remarkable consistency in rates of toxicity and death between these studies and previous reports of toxic effects within phase I studies [1, 2, 5, 7], although some smaller series have reported higher toxicity rates of over 30% [8, 9]. This consistency in toxicity rates is seen despite the use of different agents and a move from the development of cytotoxics to the development of MTAs, although Wheler et al. [2] did find that toxicity rates were slightly higher in patients receiving cytotoxics. Interestingly, the toxicity rates reported here are lower than rates seen on later phase trials, despite the rigorous data—capture on phase I trials. This may reflect the selection of a fitter patient population for phase I studies, the probability that some patients on a phase I trial are receiving sub-therapeutic doses or a combination of these factors.

In both studies, the authors attempted to identify factors that might predict patients who are at higher risk of toxicity, and in both studies, poor performance status was determined to be associated with increased rates of severe toxicity (more than double those seen in patients with good performance status) [1, 2]. It is sometimes difficult to restrict entry on to phase I studies to patients with good performance status, particularly when an exciting new agent is under evaluation. However, these studies confirm that the risk: benefit ratio may be lower in patients with poor performance status. In addition, inclusion of patients with poor performance status in phase I protocols may lead to the observation of more dose-limiting toxicities (DLTs) and the classification of a lower dose as tolerable, with a subsequent detrimental effect on further clinical development of a new agent.

In addition, both studies showed that the RMH score (albumin < 35 g/l, LDH greater than the upper limit of normal and > 2 metastatic sites), which was designed to identify patients less likely to benefit from entry on to a phase I study in terms of response [10], did not predict subsequent toxicity. The addition of performance status (which predicts toxicity) to the RMH model does not result in any significant improvements in terms of predicting survival following entry on to a phase I trial, but poor performance status may be associated with early trial discontinuation [4]. Therefore, the studies published here can be used, in conjunction with other recent studies, to help to better inform discussions with patients about entry on phase I studies; in particular, as to the possibilities of toxicity, response and likely prognosis. This information is vital if patients are to make informed decisions about entry on to a phase I study [11].
Another ethical issue encountered in the conduct of phase I studies is that unfortunately we know that patients recruited early in the trial may be exposed to sub-therapeutic doses of an agent [12, 13], while being required to undertake the frequent medical evaluations and investigations that are integral to a phase I study [14]. Minimising the number of patients exposed to sub-therapeutic doses is an important component of the study design [12]. The possibility of starting a phase I study with too low a dose has to be set against the potential risks to the patients of starting at higher doses, which could cause severe or irreversible toxicity. This is a particular concern if the study is a First-Into-Man study of a new target. Presently, starting doses are calculated following animal toxicology studies according to guidelines published by the regulatory authorities [15, 16]. As it is on average taking five dose levels to reach the recommended phase 2 dose (RP2D) [13, 16], higher starting doses may reduce patients exposed to sub-therapeutic levels. It may be that the regulatory guidelines need to change in the era of developing MTAs.

Intra-patient dose escalation has been suggested as a potential measure to reduce the ethical issues surrounding exposure to sub-therapeutic doses [5, 17]. However, as MTA toxic effects may take several cycles of therapy to appear [18], intra-patient escalation following one cycle of therapy may lead to the risk of excess toxic effects and does not appear to lead to more rapid determination of the RP2D [5, 17]. The use of single patient cohorts and rapid dose escalations in early cohorts on a phase I study, if minimal toxicity is observed, may be one way to reduce the number of patients receiving therapies at a level that is never going to be associated with a therapeutic benefit [12].

The other major lesson to be learnt from these studies is the changing toxicity patterns that are encountered by patients receiving treatment with MTAs. Less myelosuppression may be seen and more gastrointestinal and constitutional effects are seen [1, 2]. Wheler et al. are to be commended for trying to determine which toxic effects are particularly associated with agents targeting particular pathways (e.g. bleeding, cardiac arrhythmias and angina in anti-angiogenic agents; altered mental status and seizures in treatment with histone deacetylase inhibitors). Identification of mechanism-based toxic effects (those associated with modulation of the target, e.g. rash with epidermal growth factor receptor antagonists) may be particularly valuable as they may predict the occurrence of similar toxic effects in other agents targeting the same pathway and also help in identifying a biologically effective dose [19, 20].

However, the different pattern of toxicity is leading to increasing difficulty in the identification of a maximum tolerated dose (MTD) compared with phase I studies assessing conventional cytotoxics. The grading of toxic effects that are now encountered, such as asthenia and anorexia, is often more subjective than the measurement of myelosuppression and determining what should be regarded as DLT less clear [21, 22]. Grading toxicity according to the Common Toxicity Criteria for Adverse Events (CTCAE) may not be the best measure of some toxic effects such as fatigue and diarrhoea [22]. From a patient’s viewpoint, grade 3 gastrointestinal toxicity may be less tolerable and have a greater impact on quality of life than grade 3–4 neutropenia or thrombocytopenia (if these are uncomplicated) [23]. As commented in both studies, it is increasingly difficult with toxic effects encountered with MTAs to decide whether it is related to the drug rather than progressive cancer or other co-morbidities [1, 2].

Withdrawal and cautious reintroduction of the agent under evaluation may be the best method to ascertain the relationship between a possible toxicity and drug exposure.

In addition, the different pattern of toxic effects may mean that changes need to be made to the definition of DLT to include long-term toxic effects [18, 21, 23]. Previous phase I studies developing cytotoxics, where myelosuppression was the DLT, may have underestimated the MTD due to the depleted bone marrow stem cell compartment that is commonly found in the heavily pretreated patients enrolled on these studies. The concern is that now phase I studies may be overestimating the MTD, as they do not pick up chronic toxicity [18, 23]. Toxic effects from MTAs may only arise after a long period of treatment or become increasingly non-tolerable after prolonged exposure, so that many patients may not be able to tolerate long term the dose initially identified in phase I clinical trials [23]. Clearly, chronic grade 2 toxicity may be intolerable for long-term dosing; however, determining rates of chronic toxicity on phase I trials may be difficult as the majority of patients progress after short periods of treatment [4]. Validated pharmacodynamic biomarkers of host toxicity where early changes can predict subsequent side-effects are urgently needed [24] and are as, or more, important than early pharmacodynamic biomarkers of response. Determining the range of tolerable biologically effective doses rather than an MTD may be vital for long-term administration of MTAs or for safe combinations with cytotoxic therapies [20].

The studies of Wheler et al. [2] and Molife et al. [1] not only help to answer the question as to the risk: benefit profile for patients considering enrolment on a phase I trial but also add significantly to the knowledge of toxicity rates, patterns of toxicity and risk factors for toxicity in this setting. This is important information both for clinicians involved in early drug development work and for oncologists discussing referral to a drug development unit with their patients.

Both studies confirm the need for judicious patient selection and show that phase I trials should be conducted within specialist units with the facilities and expertise to safely manage toxic effects [14]. In addition, it is mandatory that drug development centres have the ability to perform the accompanying translational work that allows the maximum information to be acquired from each patient who enters a phase I trial. Ongoing collaborations are needed between drug development units to monitor patterns of toxicity, to try and reduce the risks as much as possible for these patients and determine whether targeting particular pathways are associated with an excess risk to patients. The studies reported here highlight the need for the continued evolution of the design of phase I trials to meet the challenges encountered in the era of MTAs and personalised medicine [20].

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