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Recommended changes to oncology clinical trial design: Revolution or evolution?

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Medical oncologists have traditionally been outside the mainstream of internal medicine, with oncology often being a separate department. In addition, there are many large freestanding cancer centres focused exclusively on oncology care. This partial isolation of the oncologist may have contributed to the evolution of diverse approaches to new drug development between oncology and other therapeutic areas. Specifically, the traditional approach to cytotoxic drug development has utilised phase I trials to determine the maximally tolerated dose (MTD) and nonrandomised phase II trials (at the MTD) to measure the rate of (complete and) partial radiographic responses. Thus, phase III has traditionally been the first randomised controlled evaluation. In contrast, other therapeutic areas (including studies of other lethal conditions without effective treatments) have primarily utilised blinded, placebo-controlled randomised trials in phase II to assess efficacy and to explore dose-response relationships.[1] Single-arm historically controlled phase II trials are rarely employed outside of oncology.

What are the reasons for the divergent evolution of trial designs between oncology and other therapeutic areas? There are many contributing explanations for this variance, including: 1) a past paucity of potential targets and drugs, 2) the traditional dogma in oncology that 'more is better', 3) the mostly predictable, reversible and dose-dependent nature of toxicities of most cytotoxic agents, 4) a ready acceptance of toxicity by both oncologists and cancer patients, 5) the belief that an observed response rate is sufficient information to guide future development, 6) an acceptance of phase II trial designs that identify ineffective agents, but do not predict for phase III success,[2] and 7) discomfort among many oncologists and cancer patients regarding the use of placebos. These attitudes, coupled with the complex life-threatening nature of the disease, led to the simple drug development paradigm described above. Unfortunately, this traditional oncology paradigm does not take advantage of the investigative tools that have the potential to promote optimisation of medication use. We believe that this difference in

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paradigms between oncology and other therapeutic areas accounts, at least in part, for the higher phase III failure rate in oncology, and also possibly the lower overall success rate.[3]

Outside of oncology, efficacy is also carefully weighed against toxicity, but more rigorously investigated by evaluation of two or more efficacious doses in phase III studies.[4-8] Thus, drug development procedures that carefully define 'optimal dose' are frequently used in other therapeutic areas. Note that 'optimal dose' in these other therapeutic areas is not defined in phase I and is not defined through the use of novel biomarkers, but is routinely determined through randomised controlled phase II and/or III trials, sometimes incorporating surrogate endpoints or previously qualified biomarkers.[9] Furthermore, demonstration of a relationship between dose or concentration and an efficacy biomarker that lies in the causal path of disease (e.g. HIV viral load) often provides plausible evidence that the drug is efficacious.[8] Dose ranging in cancer trials has been hampered by the absence of a validated biomarker that is also a continuous variable, such as blood pressure or flow rate, although change in tumour size has been recently suggested to be a potential efficacy biomarker.[10]

For some therapeutic areas, the US Food and Drug Administration has developed Guidance Documents to assist industry in designing clinical trials and development programmes. Drug development approaches employed in rheumatoid arthritis are of particular interest, as there are many overlapping targets with cancer.[11] In the FDA Guidance for rheumatoid arthritis, it is noted that, 'Dose finding is a central challenge of phase 2 development. Once a reasonably safe range of doses has been established, randomized, parallelarm dose comparison trials are ordinarily recommended.'[12] Of course most cancer patients are more likely to die of their disease in a shorter period of time than patients with rheumatoid arthritis and this may affect trial design.

Given this background, what is the basis for the recommendations from the Task Force on Methodology for the Development of Innovative Cancer Therapies (MDICT), the focus of this editorial.[13,14] The MDICT was appointed by the NDDO Research Foundation (www.nddo.org), a private organisation engaged in the conduct of research and the organisation of scientific meetings, for the purpose of addressing methodological issues created by a change in oncology paradigm — from cytotoxic agents to 'molecular targeted therapies' (or from drugs primarily targeted at DNA to those primarily targeted at cellular signalling). The recommendations reported by Booth and colleagues stem from two meetings, one each on phase I and II design.

While we view many of the MDICT recommendations regarding phase I trials as valid, it is important to discuss some of the caveats. The phase I recommendations emphasise the importance of defining the maximally tolerated dose, with incorporation of biomarker studies only as needed to assist with further development. The strongest case made by the authors for biomarkers in phase I trials is for the PARP inhibitor, AG-014699.[15] We agree that demonstration of proof of mechanism is important for agents of this nature, if the biomarker results will be used to make the 'go/no-go' decision, as suggested by Littman and Williams.[16] Pharmacodynamic biomarkers are theoretically of value as an aid to overall decision-making, although the benefits of incorporating these advanced technologies have not yet been demonstrated, particularly in regard to identification of an optimal dose and/or schedule. Furthermore, too much information can impair the solution of complex problems,[17] and biomarker studies may add significant cost and complexity to phase I clinical trials.[18] Given these concerns, we need to recognise that a more realistic outcome of a phase I trial is identification of a safe range of candidate doses, with the optimal dose identified in dose-ranging phase II studies (ideally with blinding), the standard paradigm in other therapeutic areas.[4,12]

Thus, we disagree with the general recommendation of Booth and colleagues[13] regarding the appropriateness of nonrandomised phase II trials, which conflicts with drug development paradigms outside of oncology.[19-21] Since some molecularly targeted oncology drugs are similar or identical to molecularly targeted non-oncology drugs,[11,22,23] their drug development programmes should logically resemble non-oncology drug development programmes, with allowances for differences in the course of the underlying disease. This potential convergence of trial designs is not a revolutionary change, but simply an evolutionary change towards standard paradigms, as described in the EMEA and FDA Guidance documents.

As emphasised by the MDICT's recommendations, some oncologists remain reluctant to utilise randomisation in phase II, often because of concerns regarding the statistical limitations of small randomised trials. However, the use of historical controls has repeatedly yielded unreliable conclusions, due to misinterpretation of the implications of rejecting the null hypothesis, as well as inadequate justification for the choice of the null hypothesis itself.[2, 24-26] In referring to the use of historical controls defined by 'general medical knowledge of outcome', ICH E10 states, 'Use of this latter comparator is particularly treacherous….' Randomised phase II trials should be designed to compare treatment effects across arms, not comparison of each arm to a historical control as proposed by Simon.[27] The results of any nonrandomised trial reflect some combination of treatment effect, random effect, biased recruitment, and unknown differences between treated and control patients. With randomisation, effects other than treatment are theoretically balanced, permitting probabilistic estimation of the treatment effect, with the magnitude of the random effects being controllable by the sample size. We strongly recommend that randomised comparative phase II trials (with dose ranging as appropriate) become a standard approach in oncology, especially for the development of drug combinations.[28] In contrast, nonrandomised phase II trials should have a more limited role, but will undoubtedly continue to be utilised when the primary drug development decision will be based on the estimation of the response rate to a single agent of unknown activity, although even in this context it may be desirable to determine the relationship of dose to response rate. Phase II trials in rare diseases will continue to be problematic, and in this context, nonrandomised phase II trials may be the only pragmatic option.

Our recommendations regarding randomisation are consistent with those of Rubinstein and colleagues[29] regarding phase II screening trials. Phase II trials are not intended to be definitive studies, but do need to have valid controls, with both type I (for positive conclusions) and type II (for negative conclusions) error rates considered in the interpretation of the results. Error will be reduced by larger sample sizes. In instances where one has less confidence in usefulness of biomarkers, a randomised phase II trial could screen therapies evaluating effects on the same clinical endpoint to be used in phase III.[7] Since the intention of phase II is to 'learn' (whereas phase III trials should 'confirm' phase II results), modelling of the relationship (potentially adjusted for biomarkers or other patient identifying factors) between dose (and/or exposure) and one or more endpoints may also be informative.[30,31] (In this case, the hypothesis being tested is that some dose is more effective than no treatment.)

Full discussion of trial design features of randomised phase II trials is beyond the scope of this editorial, although careful consideration should be given to critical design issues such as: 1) number and separation of dose (or exposure) levels, 2) adaptive versus fixed designs, 3) the primary endpoint, 4) enrichment strategies, 5) the potential use of crossover or discontinuation designs and 6) type I and II error. We believe that the standard oncology 'cookie cutter' approach to phase II design should evolve to a more individualised approach, potentially aided by clinical trial simulation.[32]

The creation of the Task Force on MDICT itself reflects the generally accepted need for a careful reconsideration of early clinical trial design in oncology. And for phase I trial design,

the level of methodological disagreement is minimal. However, the complexity of optimising phase II trials that will best predict for phase III success should not be underestimated.

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