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Early phase clinical trials—are dose expansion cohorts needed?

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Abstract

Dose-expansion cohorts (DECs) enable investigators to identify potentially effective drugs, for specific patient populations, in a single trial by assessing antitumour activity as early as possible. We discuss how the objectives, design and interpretation of DEC have evolved, and how DECs are changing the landscape of early drug development.

In the past few years, the landscape of early drug development in oncology has changed substantially. Under the old paradigm, investigational drugs were tested in a phase I trial with a small, heterogeneous patient population, to identify a safe dose before moving into disease-specific, phase II testing, in which antitumour activity was assessed. This paradigm works well when few drugs are available for testing at any given time; however, technological advances have enabled numerous promising compounds to be identified that all need to be tested expeditiously in clinical trials. Moreover, molecular testing has enabled clinical investigators to potentially increase the clinical benefits for specific patient subgroups, based on molecular characteristics. These changes have stimulated the need to assess antitumour activity as early as possible in the process of drug development, resulting in the emergence of phase I trials with larger patient populations, which are designed to obtain preliminary evidence of efficacy as well as safety.[1] The challenge is how to best identify which drugs work, and in which patient populations, while using the fewest resources.

Phase I trial designs increasingly go beyond their former focus on safety, and aim to identify the most-promising agents by adding dose-expansion cohorts (DECs), before moving to phase II testing.[2,3] Such phase I trials now frequently include a dose-escalation phase that determines the maximum tolerated dose (MTD), followed by a dose-expansion phase to determine the recommended dose. Patient eligibility criteria for DECs are often narrow and focus on specific molecular characteristics, disease types, or both. DEC trials have various objectives: confirming that a safe level of drug exposure has been established; obtaining preliminary evidence of efficacy; and identifying specific patient subgroups that might

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derive particular benefits from the investigational treatment.[3] DECs enable investigators to identify drugs that work best for specific patient populations in the context of a single trial, rather than using separate phase I trials and multiple phase II trials in specific patient populations. The costs and administrative burden associated with conducting separate trials can be greatly reduced, and the resources saved can be allocated to testing other promising compounds. Important questions remain: are DECs efficient, and to what extent do they help clinicians decide which drugs to take forward for further testing?

Current DECs typically add an additional number of patients (usually ≥12) who are all treated at the established MTD based on predose-expansion data. Use of such cohorts can reduce the uncertainty in estimating the MTD, which is especially relevant in trials of combination regimens involving targeted agents.[1] Experimenting with multiple doses to better evaluate the dose–response curve is also a rational approach.[4] Other trial designs can address certain questions, such as factors contributing to differing levels of treatment tolerance, or whether variations in tolerance correspond with differences in efficacy.[4–7] DECs have emerged to address multiple objectives, including assessing drug efficacy within separate patient subpopulations.[3] For example, Topalian *et al.*[8] addressed the safety, activity and immune correlates of the anti-PD1 antibody nivolumab. In this study, disease-specific patient cohorts were selected to further assess the safety, dose–response parameters and clinical-activity profile of nivolumab. Patients in the five expansion cohorts (16 patients per cohort) received 10 mg/kg of nivolumab for the treatment of non-small-cell lung cancer, advancedstage melanoma, renal-cell cancer, metastatic castration-resistant prostate cancer, and colorectal adenocarcinoma. Additional non-MTD expansion cohorts (with up to 16 patients per cohort) were enrolled, on the basis of initial signals of activity, for the treatment of melanoma (initially at doses of 1.0 and 3.0 mg/kg of nivolumab, followed by cohorts randomly assigned to 0.1 mg/kg, 0.3 mg/kg, and 1.0 mg/kg of nivolumab), lung cancer (patients with the squamous or nonsquamous subtypes randomly assigned to receive a dose of 1.0, 3.0 or 10 mg/kg of nivolumab), and renal-cell cancer (at a dose of 1.0 mg/kg of nivolumab).[8]

This phase I study [8] had a successful outcome: notable antitumour activity was observed, with a favourable safety profile, across all dose levels. Randomization enabled investigators to compare both safety and efficacy across multiple dose levels and disease types. The design included the possibility of early cessation of the trial and the sample size was justified for each cohort, based on the width of the confidence interval for the objective response rate obtained within the cohort. However, this trial used an ad-hoc design involving five amendments and 14 expansion cohorts. Amendments to include additional DECs or to evaluate overall survival[9] were prompted by initial evidence of antitumour activity, which when viewed from a statistical perspective, raises the issue of false discovery: increasing the number of statistical comparisons increases the risk of a false positive result, in this case a cohort with a false signal of antitumour activity of nivolumab. The study design did not aim to control for the possibility of false-positive or false-negative findings, which might lead to inaccurate conclusions in certain subgroups. In the Topalian study,[8] promising antitumour activity occurred, with very limited adverse effects and thus, there were no ethical concerns in enrolling patients. In general, modifying the design of a study with multiple amendments,

such as changes in patient eligibility criteria or the inclusion of initially unspecified subgroup analyses, raises ethical and scientific considerations that affect the validity and interpretation of the data. In addition, amendments often lead to delays in protocol activation and an increased administrative burden. The exploratory nature of DEC studies in general allows for a higher rate of false-positive or false-negative errors compared with later-phase trials; thus, these comparisons are often more descriptive. Many promising agents and combination regimens are competing to enter the pipeline for drug development; therefore, understanding the risk projections derived from DECs is imperative. Trials with DECs of multiple subgroups and a small number of patients can still quantify this risk, albeit the risk increases with smaller sample sizes. Findings of this study suggest high antitumour activity in most of the subgroups,[8] and these findings have been confirmed by further testing;[4,9] however, the underlying methodological issues must be addressed before future DEC use. The current approach of enrolling large numbers of patients across multiple DECs is insufficiently structured to enable reliable interpretation of the data and provide valid inferences upon completion.

Many clinical trial protocols contain no scientific rationale to justify the sample sizes of DECs. How many patients are needed to answer all three questions (efficacy assessment, identification of subgroups, and selection of drug and MTD) with sufficient confidence to warrant further testing? By 'confidence' we mean the ability to interpret the findings with a low risk of either a false-positive or false-negative result, or at least with a clear understanding of how large these errors are. When the aim of adding DECs goes beyond safety assessment, justifying the design becomes essential, especially when projected enrolment for DECs, per cohort, approaches the traditional cohort sizes of a phase II study. For example, for studies with a sample size of 25–35 patients, if the treatment effect is insufficiently large, the false-positive and false-negative error rates will be higher than those of typical phase II studies. Early stopping rules for lack of efficacy would minimize the number of patients receiving an ineffective drug in DECs. Alternatively, if the aim is to conduct preliminary efficacy assessments in particular subgroups, methods should be used that provide some degree of statistical control by quantifying the errors associated with decisions to proceed with, or halt a study.[10]

This objective can be achieved by contrasting pairs of hypotheses on the basis of accumulating evidence. For example, the hypothesis that 'the drug is both efficacious and safe' is contrasted with 'the drug is not efficacious' or 'it is efficacious but not safe'; 'inconclusive' would be the answer when the error rates cannot be controlled. In this situation, investigators would need to treat more patients in a particular cohort. Reasons behind an 'inconclusive' result include current data showing antitumour activity at a poorly tolerated dose, or data showing a trend towards a lack of antitumour activity with a large amount of uncertainty in what has been observed. Given an inconclusive result, investigators can decide whether to enrol more patients in a particular cohort, halt accrual, or consider focusing on a particular disease or targeted population in a specific DEC. For studies with 15–25 patients in each DEC, when the expected efficacy of the experimental agent in a targeted population is not known, and hence standard power calculation is not feasible, we suggest that investigators provide a probabilistic calculation of how the observed activity

compares with the historical control rate—meaning an efficacy estimate that is typically a response rate obtained from a completed study in a comparable patient population.

From current examples, observations on the evolution of drug development, and general clinical considerations, we believe that DECs are needed. This approach provides a more refined estimate of the MTD than that obtainable from a traditional phase I study designed to guide dose escalation using either a sophisticated model-based design or the simple 3 + 3 design.[2] Phase I DECs take investigators into territory that was the remit of phase II studies by looking for disease-specific efficacy in selected patient populations. DECs also go beyond standard phase II objectives by examining histology-specific or biomarker-specific subgroups, and their possible interactions, which is beyond the capacity of standard phase II designs. A phase I trial with a DEC design does not yet answer the questions that a phase I trial followed by a phase II trial would, although this approach has the potential to do more than the two designs combined.

In summary, the phase I plus DEC design is here to stay, and is challenging our thinking of the old phase I and phase II study designs and ultimately, our overall approach to drug development. Researchers must determine how to optimally use DEC data in order to identify the most-promising patient populations and doses to possibly take forward to randomized phase II or III trials.

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