CLINICAL INVESTIGATION

in

The benefits of including expansion cohorts in Phase I oncology clinical trial design

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The primary objective of a Phase I study is to determine the recommended Phase II dose (RP2D) of a new drug or combination of agents. Increasingly, these studies are enrolling additional patients once the RP2D has been determined to further characterize the toxicity and efficacy profile, as well as the pharmacokinetic (PK) and pharmacodynamic (PD) properties of the studied agent/combination. Typically referred to as an expansion cohort, this design is often employed in specific patient populations with either a particular histology or molecular aberration.

The advent of expansion cohorts has been driven by the need to collect additional information on certain properties of the investigational agent. The shift away from traditional chemotherapeutics to molecularly targeted agents (MTAs) has presented new challenges in Phase I trials. As MTAs may not have dose-dependent toxicities, early phase studies may not have the optimal operating characteristics to accurately identify important toxicities or the RP2D in some instances. To mitigate these limitations, various design adaptations have been employed, such as model-based dose-escalation methods, incorporating chronic or delayed toxicities when determining the RP2D, more comprehensive PK/PD assessments and the inclusion of expansion cohorts [1–3]. Furthermore, the decision to continue development of a drug into later phase studies may be based on safety, efficacy or PK/PD measures; and all of these parameters are perhaps better interrogated by the inclusion of an expansion cohort. These go/no-go evaluations aim to prevent nonefficacious therapies from consuming precious development resources, while permitting potentially active drugs to be tested in Phase II or III studies.

Beyond these general considerations, more specific aspects of expansion cohorts have been evaluated in a recent systematic review. This study analyzed Phase I single-agent trials from 2006 to 2011 and reported several observations [4]. Approximately a quarter of Phase I trials observed in this review included at least an expansion cohort, and the rate of expansion cohort utilization increased from 12 to 38% over this time period. The main objectives for including an expansion cohort were commonly for safety/toxicity (80%) and efficacy (45%), although 25% of studies did not explicitly declare the objectives of the expansion cohort in their final publication [4]. The use of expansion cohort was meaningful with regards to safety/toxicity as in 13% of the studies observed, the RP2D was revised due to the occurrence of previously undetected serious adverse events [4]. Expansion cohort utilization may be useful to strengthen preliminary findings on efficacy but it is worth noting in this particular review that if antitumor activity was not observed in the dose-escalation phase, it was unlikely that it would then occur on expansion phase of the study. This review also recommended that expansion cohorts must address a specific question with a statistically justified sample size and predefined criteria if being used to inform go/no-go decisions about the development of a drug. Appropriate design and implementation of expansion cohorts will ensure that the maximum benefit is garnered from such strategies.

Aaron R Hansen
Princess Margaret Cancer Centre, University Health Network, Division of Medical Oncology & Hematology, Toronto, ON, Canada
and
Department of Medicine, University of Toronto, Toronto, ON, Canada

Albiruni RA Razak
Author for correspondence:
Princess Margaret Cancer Centre, University Health Network, Division of Medical Oncology & Hematology, Toronto, ON, Canada
and
Department of Medicine, University of Toronto, Toronto, ON, Canada
Tel.: +1 416 946 4501 (ext 5634)
Fax: +1 416 946 4467
albiruni.razak@uhn.ca

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A statistical simulation has demonstrated that the use of expansion cohorts improved the accuracy of the RP2D when compared with the maximum tolerated dose (MTD) defined after the dose-escalation phase [5]. In approximately 50% of trials, the MTD was revised following observations from the expansion cohort; and of these revisions 30% were changed to the true MTD and 50% were altered to within one dose level of the true MTD [5]. While these estimates are not based on actual clinical trial outcomes, they do suggest that re-evaluation of the MTD with information gathered from the expansion cohort is warranted. Currently, there is no accepted methodology to re-assess the MTD in the context of an expansion phase of a study, although several approaches have been proposed. These revision methods include: retrospectively combining the safety data from both phases; prospectively utilizing safety and or efficacy data collected in the expansion cohort with a dose-seeking algorithm to adjust the dose level based on observed toxicities or antitumor activity; testing multiple dose levels at the expansion wherein patients are randomized to different dosage arms; and testing different doses in different patient populations to determine if different groups have separate MTDs [5].

In addition to enhanced recommended dose accuracy, the increased sample size from expansion cohorts increases the probability of observing a rare adverse event. By including a further 37 patients in a study with 45 enrolled, the likelihood of detecting a toxicity that occurs with a 5% frequency will increase from 90 to 99% [6]. Whereas we acknowledge that the inclusion of an expansion cohort of a considerable size would consume additional resources, when balanced to the fact that it may prevent failed studies in later stages, these investments are deemed potentially useful and effective.

In this context, expansion cohorts should be purposefully integrated into Phase I studies and not routinely. These additional patients should only be included if a specific question supported by a robust scientific rationale is being addressed. Furthermore, the size of the cohort must be statistically justified to provide some level of confidence for data interpretation. For example, a study drug that displays no clinical activity with no PK or PD marker would probably not warrant an expansion cohort.

Despite these scenarios, the majority of trials could appropriately utilize an expansion cohort to refine both RP2D and adverse event detection. The clinical and design benefits of expansion cohorts are emerging as more trials adopt this methodology. Expansion cohorts should not be used to usurp a properly conducted Phase II trial, however, they can be influential in making go/no-go decisions for drug development. In order to capitalize on the impact of expansion cohorts they must be correctly applied to Phase I trials.

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References

1 Le Tourneau C, Lee JJ, Siu LL. Dose escalation methods in Phase I cancer clinical trials. *J. Natl Cancer Inst.* 101(10), 708–720 (2009).

2 LoRusso PM, Boerner SA, Seymour L. An overview of the optimal planning, design, and conduct of Phase I studies of new therapeutics. *Clin. Cancer Res.* 16(6), 1710–1718 (2010).

3 Postel-Vinay S, Le Tourneau C, Olmos D *et al.* Towards new methods for the determination of dose limiting toxicities and recommended dose of molecularly targeted agents. Presented at: *European Cancer Congress (ECCO-ESMO-ESTRO)*. Amsterdam, The Netherlands, 27 September–1 October 2013.

4 Manji A, Brana I, Amir E *et al.* Evolution of clinical trial design in early drug development: systematic review of expansion cohort use in single-agent Phase I cancer trials. *J. Clin. Oncol.* 31(33), 4260–4267 (2013).

5 Iasonos A, O'Quigley J. Design considerations for dose-expansion cohorts in Phase I trials. *J. Clin. Oncol.* 31(31), 4014–4021 (2013).

6 DeMichele A, Berry DA, Zujewski J *et al.* Developing safety criteria for introducing new agents into neoadjuvant trials. *Clin. Cancer Res.* 19(11), 2817–2823 (2013).