Number of Seamless Clinical Trials in Oncology Has Risen Recently

Increase in seamless trials was associated with increased number of cancer therapeutics approved by the FDA

PHILADELPHIA —The number of early-phase trials in oncology that adopted a seamless approach, as opposed to a traditional trial approach with defined phase I, II, and III plans, is rising, with data from the majority of them presented after 2014, according to a study presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, held Oct. 26-30.

"Seamless trials are combined studies where, instead of conducting the conventional phases I, II, and III, the trial adapts and expands based on the results of interim data," said Pedro Barata, MD, MSc, Experimental Therapeutics Fellow at the Cleveland Clinic in Ohio. "First-in-human phase I studies adopting a seamless approach have the flexibility to expand rapidly with multiple cohorts enrolling hundreds of patients in large expansion cohorts, which tends to save time in the drug development process."

The development of more effective therapies and improved patient selection with biomarker discovery in the last decade has led to calls to expedite the drug development process, explained Barata. Consequently, there has been an expansion of creative trial designs that could provide preliminary signals of efficacy and sufficient data to make the tested therapeutics eligible for early approval.

Although seamless design–based early-phase trials are expanding, their prevalence, clinical design, and characteristics are unclear, Barata noted. He and his collaborators conducted a multi-institutional study to evaluate these factors and their success, by measuring the number of drugs tested in these trials included in the expedited programs run by the U.S. Food and Drug Administration (FDA).

The researchers reviewed all clinical trial abstracts presented at the American Society of Clinical Oncology annual meetings between 2010 and 2017. Seamless trials were defined as any early-phase studies that enrolled 100 or more patients. Of the 1,786 phase I/II trials identified, 3 percent (51 trials) were seamless trials, but accounted for 15 percent of all the patients enrolled. Seamless trials had up to 13 expansion cohorts and data from 65 percent of them were presented after 2014.

Overall, 50 investigational new drugs were tested in early studies using a seamless approach, which included targeted therapies, immunotherapies, antibody-drug conjugates, and chemotherapies, tested as single agents or in combinations.

Data showed that the FDA had granted accelerated approval for eight therapeutics (16 percent) and a priority review for a ninth agent tested in seamless trials. "It is estimated that only 5 percent of oncology drugs that enter human testing ultimately receive FDA approval, therefore, our findings seem to confirm the higher success rate of the drugs studied with the seamless approach," Barata said.

The researchers also found that of the 29 studies published from the 51 seamless trials, 69 percent of them did not have a plan for statistical analysis to calculate the sample sizes of the expansion cohorts.

"Whenever a pre-planned statistical plan is missing, the value of the data is limited, being simply descriptive and demanding further validation," explained Barata. "The numerous, nonrandomized cohorts in each trial and modifications to the study design with multiple amendments put these studies at a higher rate for false-positive or false-negative errors compared with later-phase trials, thus affecting the validity and interpretation of the data."

While seamless studies offer rapid access to anticancer drugs via accelerated FDA approval, Barata cautioned that concerns, such as potential exposure of patients and drug developers to avoidable risks due to lack of safety monitoring system, communication challenges between pharmaceutical companies, investigators, and regulators regarding frequent protocol modifications, and potential limitations with maintenance of data quality and statistical integrity with these designs need to be addressed in order to improve the quality of this approach and outcomes.

Limitations of the study include its retrospective nature, the inclusion of studies from a single national meeting, and limited access to trial information (meeting abstracts) and not the complete trial protocols.

Barata declares no conflicts of interest.

Abstract: A100

Presentation Session: PO.A11 – Clinical Trials; Saturday, Oct. 28; 12:30-4 p.m. ET; Hall E

Title: Seamless phase I/II clinical trials in oncology: retrospective analysis of the last 7 years

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Introduction: Drug development has evolved from the conventional sequence of three-phase clinical trial process to a seamless approach of adding cohorts to first-in-human trials to investigate both safety and efficacy in various cancers. In this retrospective study, we evaluated the prevalence of large early-phase studies in adult cancer patients; described the clinical characteristics, design, and statistical plan of these studies; and identified which investigational drugs using this seamless strategy were included in the accelerated approval program by the Food and Drug Administration (FDA).

Methods: All abstracts presented at the American Society of Clinical Oncology (ASCO) annual meetings from 2010 to 2017 were reviewed. Clinical studies conducted in the pediatric population as well as abstracts reporting trials in progress were excluded. Seamless clinical trials were defined as any phase I/II studies with a sample size of 100 or more patients. The Center for Drug Evaluation and Research (CDER) drug approvals report was used to access the list of drugs included in the accelerated approval program by FDA.

Results: We identified a total of 1786 early-phase trials enrolling more than 57,500 patients with malignant neoplasms. More frequently these studies included patients with advanced solid tumors (87%) and targeted therapy and immunotherapy agents were investigated in 64% and 15% of the cases, respectively. Of the 1786 trials, 51 were identified as seamless phase I/II with a sample size of 100 or more patients, representing only 3% of the total number of trials (n=1786) but 15% of the total number of patients (n=57,559). These seamless trials had a median number of 3 (1-13) expansion cohorts and a higher fraction (65%) were presented in the last 3 years (2014-2017), compared with 35% of the studies with results presented between 2010-2013. Fifty active investigational new drugs (67% targeted therapy, 18% immunotherapy, 10% antibody-drug conjugate, 2.0% chemotherapy, 3.9% other) were studied as single agents (53%) or in combination with other therapies (47%). Of the 51 identified large seamless phase I/II trials, only 29 (57%) studies had published results. Further, of these 29 studies, a planned statistical analysis for the calculation of the expansion cohorts' sample-size was not available in 69% of the cases. The overall rate of significant (grade 3-4) adverse events was 49% (range, 0-100%), and at least one toxic death was reported in 5 of these studies. The pooled response rate (CR+PR) per study was 20% (range, 0.9-77). Considering the group of drugs studied in the 51-seamless phase I/II trials identified here, the FDA granted accelerated approval to 8 drugs and 1 other agent was given priority review.

Conclusions: Approximately two-thirds of the studies identified were presented after the year 2014, suggesting an increased use of the seamless approach. While the high rate of accelerated approvals granted by the FDA endorses the observed preliminary clinical benefit of these drugs, the absence of a prespecified statistical plan is a weakness of most of the published studies

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