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Editorial

EDITORIAL

Defining a Clinically Meaningful Benefit in Cancer Clinical Trials: From the Perspectives of the Clinical Trialist, Patient, and Society

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In an era of value-based medicine, it is increasingly important to design clinical trials of new therapies that not only show statistically significant benefits compared with current standard therapies but also yield an adequate magnitude of benefit to be deemed "clinically meaningful." In a 2014 recommendation, the American Society of Clinical Oncology (ASCO) indicated that clinical trials studying targeted therapies for metastatic solid tumors need to demonstrate a 20% or more relative improvement in overall survival (OS) (ie, hazard ratio [HR] $\leq$0.8) to be considered to have a clinically meaningful benefit (1).

The article in this issue of the journal by Lawrence et al. addresses one aspect of this goal focusing on the effect size (2). The authors analyzed the hypothesized and observed effect sizes from phase III trials of targeted agents and immunotherapies for metastatic cancers from 2005 to 2015. Although 98% of the trials with a primary endpoint of OS were designed to detect an HR threshold of 0.8 or lower, 53% of trials with a statistically significant improvement in OS had an observed effect size less extreme than hypothesized. Thus, 23% of these trials showed statistically significant differences in OS that were not deemed "clinically meaningful" (ie, HR $>$0.8). The authors concluded that many trials were overpowered and that future phase III trials should not be designed to yield observed results that are "of dubious clinical importance."

From the perspective of the clinical trialist, it seems that almost all the trials included in the analysis by Lawrence et al. were designed appropriately with a reasonable range of estimated effect sizes, despite their inception many years before the 2014 ASCO recommendations. Regarding the critique from the authors described above, it should be emphasized that randomized clinical trials need equipoise to be ethical. If the intervention arm of phase III trials were consistently expected to yield large magnitudes of benefit and/or success rates of establishing superiority much higher than 50%, then many patients may be subject to an unethical random assignment to the control arm of these trials.

Similarly, from the patient's perspective, enthusiasm for participating in randomized trials would likely decrease dramatically in a world where hypothesized benefits in trials were almost always correct. Perhaps patients would be more likely to drop out when randomly assigned to the control arm. After all, how many patients would want to receive a control intervention that is, say, 90% likely to be inferior to the other treatment arm? How many physicians would want this for their patients? Although blinding/placebo could sometimes prevent patients from knowing the treatment arm, it is often imperfect due to different modes of administration of the therapies in the two arms and/or different toxicity profiles. Further, if a trial were designed to show a 20% hypothesized OS improvement for a new therapy but only a 10% improvement is demonstrated at completion of the trial, many patients would still consider this to be "clinically meaningful" for them depending on their goals of care.

Disease-specific endpoints such as OS and progression-free survival are not the only important outcomes for patients. Although the magnitude of OS benefit in a trial is important, with smaller differences being less clinically meaningful, this needs to be considered in the context of the patient's quality of life and treatment-related side effects. A new therapy showing a small OS benefit or even no OS benefit, but meaningful improvement in the patient's quality of life due to longer cancer control and/or reduced toxicity compared with conventional therapy, would likely be desirable for patients. On the other hand, some patients may not choose to receive a new therapy that meets the 20% relative OS improvement threshold but with a small absolute OS benefit and with the tradeoff of major toxicities.

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After trials have been appropriately designed and conducted including all relevant endpoints, the valuation of new therapies often relies on society's perspective. With a continued rise in the cost of medical care, society must weigh the magnitude of benefit of new therapies against their costs. The term "value" is often used, defined as the health outcomes achieved per monetary expenditure (3). Many European countries, including the United Kingdom, France, and Germany, have their respective reviewing bodies to assess value of new therapies, integrating clinical and financial considerations, which ultimately affect approval of therapies and therefore patients' access to them. Cost effectiveness is specifically considered in the United Kingdom, for example; it makes intuitive sense that therapies with smaller OS benefit should not be arbitrarily deemed "not clinically meaningful," but the magnitude of benefit should be part of the value assessment of the therapy. In the United States, where cost effectiveness is not formally considered in the drug approval process, value frameworks such as the one from ASCO (4) provide guidance to clinicians in their treatment selection process.

The process of developing, testing, and approving new therapies to continually improve the care and outcomes of cancer patients is complex and involves many stakeholders, including patients, clinicians, and regulatory bodies. Because of limited resources, only the most promising new therapies—ones most likely to yield clinically significant benefits—can be tested in phase III trials. However, defining whether the demonstrated benefit is "clinically meaningful" depends on the perspective, which cannot be encapsulated with a single threshold or metric.

Notes

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