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Outcome measures of phase III anticancer drug trials in China

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To the Editor: Phase III clinical trials have been used to provide evidence in support of the approval of most new agents in the treatment of cancer.[1] The selection of the primary endpoint is critical to the outcome of phase III clinical trials and the launch of the cancer drug. In the present study, we performed a cross-sectional study to describe the endpoint information and analyze the trends over time in the research and development of cancer drugs tested in phase III clinical trials in China.

The dataset and method used have been previously described.[2] In brief, we performed a cross-sectional study of trials on the National Medical Products Administration (NMPA) Registration and Information Disclosure Platform for Drug Clinical Studies that were registered between January 1, 2013, and December 31, 2019. For trials initiated before 2013 but for which the related new drug application was unfinished, registration was required to be done retrospectively.

After searching and screening, 1992 trials of cancer drugs were identified [Supplemental Figure 1, http://links.lww.com/CM9/B476]. First, we excluded those that were not stage III trials ($n = 1489$). Second, 103 of these 503 phase III anticancer clinical trials were subsequently excluded from this study for various reasons. Third, data correction and reassignment were performed. Primary endpoints were classified as single or multiple endpoints, and overall survival (OS) or surrogate endpoints (including radiology-based endpoints, such as time-to-event endpoints and tumor-response endpoints, pathology-based endpoints, and blood-based endpoints) were classified according to the Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics released by the US Food and Drug Administration (FDA).

For descriptive analyses, the number (%) was used for qualitative variables. The χ^2 test was used for subgroup comparisons of single/multiple endpoints and OS/surrogate endpoints. We analyzed the 12-year trends in our selected indicators, including OS, surrogate endpoints, single endpoints, and multiple endpoints, using the Mann-Kendall test. The annual rate of change was calculated for each indicator. The year of a trial was defined by the date of the first ethical review. All statistical analyses were performed with SAS software 9.4 (SAS Inc., Cary, N.C., USA).

From 2008 to 2019, 400 phase III anticancer clinical trials were registered. Of all 400 clinical trials, 336 used a single endpoint as the primary endpoint. Progression-free survival (PFS), OS, objective response rate (ORR), and disease-free survival (DFS) were the top four endpoints, accounting for 44.6% (150/336), 28.9% (97/336), 10.4% (35/336) and 7.1% (24/336), respectively. Among the 64 trials that used multiple endpoints, OS and PFS, ORR and best of response (BOR), and OS and ORR were the top three multiple endpoints, accounting for 73.4% (47/64), 12.5% (8/64) and 6.3% (4/64), respectively [Supplementary Table 1, http://links.lww.com/CM9/B476]. A total of 154 trials (38.5%) used OS as one of the primary endpoints, and 73.8% (295/400) used a surrogate endpoint. Of the 295 trials that used surrogate endpoints, radiology-based endpoints accounted for 70.3% (281/

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400), pathology-based endpoints accounted for 2.3% (9/400), and blood-based endpoints accounted for 2.0% (8/400).

The proportion of trials using a single endpoint as the primary endpoint significantly decreased from 100% (1/1) in 2008 to 78.1% (57/73) in 2019 (average annual growth rate = −2.04%, P <0.01), and the proportion of trials using multiple endpoints as the primary endpoint significantly increased from 0% (0/1) in 2008 to 21.9% (16/73) in 2019 (average annual growth rate = 2.0%, P <0.01) [Figure 1]. As a single endpoint, the proportion of trials using OS as the primary endpoint increased from 0% (0/1) in 2008 to 41.7% (20/48) in 2017 and then decreased to 12.7% (7/55) in 2019 (average annual growth rate = 1.13%, P = 0.11). The proportion of trials using a surrogate endpoint as the primary endpoint decreased from 100% (1/1) in 2008 to 58.3% (28/48) in 2017 and then increased to 87.3% (48/55) in 2019 (average annual growth rate = −1.13%, P = 0.11).

Clinical trials of immunotherapy drugs and targeted drugs preferred multiple endpoints (all P <0.05) [Supplementary Table 2, http://links.lww.com/CM9/B476]. Domestic studies preferred single endpoints more than global studies (P <0.0001). Trials with data and safety monitoring boards preferred multiple endpoints more than trials without data and safety monitoring boards (P <0.0001). Trials of chemical drugs or traditional Chinese drugs/natural drugs preferred single endpoints more than trials of biological products (P <0.0001).

Neoadjuvant/adjuvant or first-line treatment trials preferred surrogate endpoints more than second- or subsequent-line treatment trials (P <0.0001) [Supplementary Table 3, http://links.lww.com/CM9/B476]. Trials for cancers with better prognosis preferred surrogate endpoints more than trials for cancers with poor prognosis (5-year survival rates <26.7%) (P <0.0001). Clinical trials of immunotherapy drugs preferred the OS endpoint (P = 0.01).

The most commonly used combination of multiple endpoints was OS and PFS. The reasons why multiple endpoints were used in the primary analysis were to increase the power of statistical tests (or reduce the required sample size) by aggregating information from multiple endpoints and to describe treatment effects more comprehensively in diseases that manifest in a multifaceted way where a single endpoint does not suffice to fully represent the treatment effect.[3] However, the selection of multiple endpoints can significantly increase the complexity of a trial. Finding a balance between trial complexity and efficiency and selecting the appropriate endpoint strategy will maximize study efficiency, advance study progress, and address clinical questions without unduly adding complexity to trial design and execution with multiple endpoints. In 2017, both the FDA and the European Medicines Agency (EMA) released draft guidelines on multiple endpoints in clinical trials. However, each component of the multiple endpoints needs to be fully identified, which is often missing in clinical trials.

For diseases with a favorable prognosis, the feasibility of clinical trial protocols may be one of the concerns regarding the primary endpoint chosen. Patients with tumors such as thyroid or breast cancer have prolonged survival, as the average 5-year survival rate is over 80% in China. Extensive follow-up at this time may not only prevent the early reporting of useful drugs but also be time- and cost-consuming. In addition, the subsequent therapy may heavily confound the survival analysis. In this context, using OS as the primary endpoint seems impractical. According to Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, the surrogate endpoints DFS and event-free survival (EFS) used as primary endpoints in the adjuvant setting for breast cancer, colorectal cancer, gastrointestinal stromal tumors, melanoma, and renal cell carcinoma seem to be well accepted by the US FDA. Our analysis provides additional evidence for this strategy, as we found that for trials in the neoadjuvant/adjuvant setting or those on tumors with an average 5-year survival rate of over 60%, approximately 90% of clinical trials used surrogate endpoints as primary endpoints.

The guidelines released by the EMA and FDA may have contributed to the increasing application of surrogate

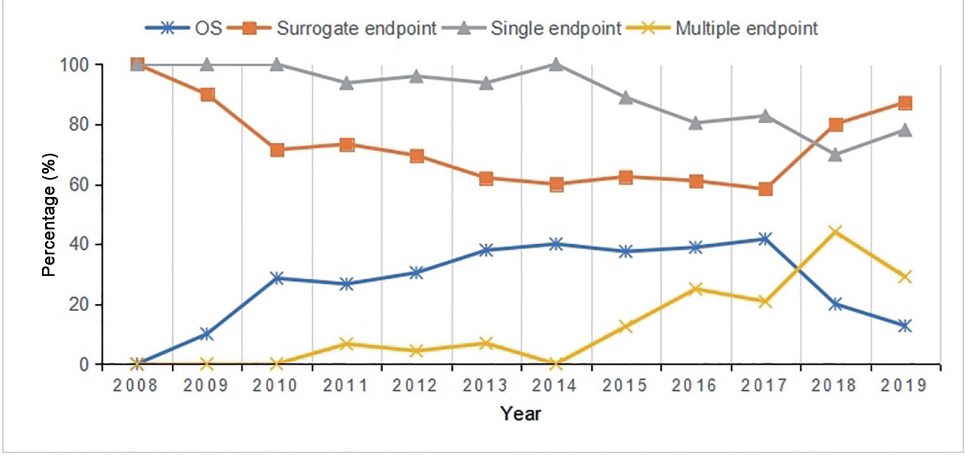

Figure 1: Time trends of endpoints of phase III anticancer clinical trials in China from 2008 to 2019. OS: Overall survival.

endpoints since 2017. It is worth noting that despite the rising trend, surrogate endpoints have not replaced OS in recent studies. The fundamental reason may lie in the heterogeneity of the correlation intensity between surrogate endpoints and OS, which may be attributed to multiple factors, such as the specific disease, context of use, magnitude of the effect, disease setting, location of metastatic sites, available therapy, and risk-benefit relationship.

The treatment strategy is one of the essential factors that influence surrogacy. There is limited evidence supporting the use of surrogate endpoints in studies of immunotherapy. Previous reports showed that there were weak correlations between PFS/ORR/disease control rate (DCR) and OS in immune checkpoint inhibitor (ICI) -treated patients,[4,5] which may be partially explained by pseudoprogression, a phenomenon specifically related to immunotherapy.[6] In contrast to chemotherapy, the effect of ICIs is not on tumor cells but on immune cells. Being treated by ICIs, some patients experience immune-related responses, such as an initial increase in the size of tumors or the appearance of new lesions, before a subsequent and sustained reduction in tumor burden occurs. Another explanation might be the residual efficacy of ICIs for a longer duration (delayed treatment effect); these drugs affect OS more than PFS even after treatment discontinuation.[7] The inferior surrogacy explains our results; immunotherapy trials used relatively fewer surrogate endpoints than nonimmunotherapy trials did.

In recent years, the NMPA has launched new priority examination and approval processes and initiated multiple actions to prevent the delayed approval of useful drugs. Approving indicated uses supported by data regarding the emerging surrogate endpoints of clinical trials may be one of the strategies to address this concern. For example, in August 2020 and 2021, the NMPA approved radium-223 and darolutamide for use in castration-resistant prostate cancer (CRPC) based on two phase III trials using metastasis-free survival (MFS) as the primary survival endpoint. In addition to radiology-based endpoints, pathology-based endpoints and blood-based endpoints are also promising emerging surrogate endpoints that can be used in trials for patients with certain disease stages or with certain tumor types. Prostate-specific antigen (PSA) is the most well-studied and proven surrogate blood-based endpoint and has been used in an increasing number of global and domestic phase 3 trials (ClinicalTrials. gov Identifier: NCT00653848, NCT04076059, NCT01695135, and NCT00182052).

Major pathological response (MPR), defined as ≤10% residual viable tumor in the resected primary lesion and lymph node tissue, is measured in samples obtained surgically after treatment and has been proven to be reliably and significantly associated with survival in multiple tumor types with heterogeneous treatment strategies in the neoadjuvant setting. It has advantages in reflecting treatment-specific antitumor activity independent of pretreatment staging accuracy and can be determined using relatively simple and inexpensive methods.[8] MPR has been accepted by NMPA as the primary endpoint of phase 3 studies to promote the approval of indications (ClinicalTrials. gov Identifier: NCT04158440, NCT04316364, and NCT04379635).

In conclusion, although favored in terms of feasibility, surrogate endpoints have not replaced OS in all areas of anticancer clinical trials. Surrogate endpoints have wider use in trials in the neoadjuvant/adjuvant setting, in trials of tumors with a favorable prognosis, and in non-immunotherapy trials. The accuracy of surrogate end points and scope of application still need to be verified by high-level evidence. Multiple new non-radiological surrogate endpoints correlated with OS are emerging, which may open up new fields deserving further exploration.

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Conflicts of interest

None.

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