Application and approval of cancer drugs in China: acceleration should be kept in progress

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Introduction

Cancer is the second leading cause of death worldwide (1). According to the latest global research, there were 17.5 million cases and 8.7 million deaths in 2015 (2). In China, cancer is the leading cause of death (3). The upgraded national epidemiological statistics indicated 4,292,000 incident cases and 2,814,000 deaths in 2015, with 36.9% of the 5-year survival rate (4). Namely, China accounts for a huge proportion of global disease burden, including a half of global gastric, liver, and esophageal cancer cases, and a third of global lung cancer cases (5).

For this, one urgent issue is a large increase in the backlog of drug registration application and approval process. According to the National Center for Drug Evaluation (CDE), the number of pending applications rose from 7,404 in 2010 to over 22,000 in 2015 (which successfully dropped to 8,200 at the end of 2016) (6,7). As measured by the China Food and Drug Administration (CFDA), the duration should be 90 working days for clinical trial registration and 150 working days for drug approval (8). However, the time in reality is far longer. The average delay time was 14 months for registering a clinical trial of an innovative drug between 2013 and 2015 (8). For imported drugs, the CFDA takes an average of 20 months to approve a new drug application; combining with average 28 months of confirmatory clinical trials required by the CFDA, approximately 5 years are needed from application to final registration approval (9). This leads to an average of 3-year lag between the US FDA and the CFDA (9).

If the process of drug application and approval were not accelerated, the backlog could be a public health issue, leading disparities between Chinese population and other regions of the world. One fundamental implication is that, patients with cancer lose opportunities to receive new proper treatments. This backlog could be pressing, especially in the new era of personalized medicine for treating cancer, with not only surgery, chemotherapies and radiotherapies, but most importantly, biomarker-driven treatments with significantly superior efficacy and drug safety (to chemotherapies), such as targeted therapies and immunotherapies.

For example, Bevacizumab, a targeted therapy against vascular endothelial growth factor, presented a significant improvement of overall survival (OS) combined with chemotherapies when comparing chemotherapies alone for recurrent or stage IIIB/IV non-small-cell lung cancer (median OS: 12.3 *vs.* 10.3 months) (10). Accordingly, Bevacizumab was approved by the US FDA in 2006 (8). However, under the requirement of the CFDA, in China it was approved in 2015, based on a confirmatory trial conducted specifically for Chinese patients (median OS: 24.3 *vs.* 17.7 months) (8,11). In this case, the gap of approval between the US FDA and CFDA is more than 7 years.

Recommendations

To accelerate the process of drug application and approval, a policy change is needed. First, direct approval for marketing should be considered according to the shared data from international randomized control trials (RCTs). Due to the large number of cancer cases based on the huge population, as well as fast-growing cancer centers competent for conducting cancer research, China has played an important role in global multicenter RCTs in the last decade. If the RCTs present new drugs with sufficiently superior efficacy

and safety to the control treatments for the Asian subgroup (especially the Chinese subgroup), the process of drug approval should not insist on the RCTs specific for only the Chinese population, regardless of the first RCTs or confirmatory trials after the first trials conducted elsewhere.

This recommendation could increase the efficiency of the approval process, dramatically reduce the budget for conducting RCTs, and subsequently provide the access of the drugs for cancer patients as early as possible. The recommendation is also a win-win solution for attracting further investment and research involvement for drug development. Ultimately, data sharing would be beneficial for cancer patients, domestically and globally.

Second, fast track should be implemented for imported drugs proved with superior efficacy and safety by RCTs without the participation of Chinese patients. For Chinese population, the dose and the indication of these drugs have to be investigated through confirmatory RCTs. However, given that their superiority has been proved according to non-Chinese participants in trials, the review and application approval for confirmatory trials are unnecessary in the original track.

Third, surrogate endpoints should be considered as the primary endpoint in RCTs, and as the available reference for considering drug approval. This recommendation could be more effective for the confirmatory RCTs. Compared with OS—the golden reference to evaluate the efficacy between the experimental drugs and the control treatments, using surrogate endpoints, such as progression-free survival (PFS), time-to-progression, and objective response rate, has the following advantages:

(I) Time saving. For example, the event of PFS could be achieved when patients either progress or die, while the event of OS could not be met until patients die, which requires a longer period of following-up (this situation would be more distinguished when early-stage cancer patients are enrolled for the RCTs instead of advanced cancer patients);

(II) Budget reduction. Normally, the cost for a RCT is far higher than any research design, mainly because a large sample size is required to achieve statistical significance. Using surrogate endpoints, budget could be reduced to some extent due to the shorter research period as well as a smaller sample size;

(III) Avoid the specific drawback of OS. To achieve the event of OS, a longer follow-up is needed, indicating a higher possibility of loss-follow-up (mostly owing to severe adverse effects caused by the treatments). A higher proportion of the loss-follow-up in either group might lead to a selection bias for the estimated treatment effect. In addition, patients who have progression after treatment assignment would receive other drugs (instead of the drugs originally assigned), possibly even the drugs of the other group (which is called crossover; e.g., patients who are originally assigned with control treatments may receive the experimental drugs after progression). Combined with loss-follow-up, these situations may either attenuate or enhance the treatment effects between the experimental and the control rather than their real effects.

The final recommendation concerns higher fees for application submission, as well as a strict penalty for falsification. These strategies would be helpful to control the volume and quality of applications, especially reducing speculative applications. Correspondingly, sufficient well-trained reviewers and administrative staff are needed (8).

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