Anticancer drug R&D of gastrointestinal cancer in China: Current landscape and challenges

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According to the latest report of cancer epidemiology published in 2022, about 1,500,000 new cases of gastrointestinal (GI) cancers were diagnosed in China, with 1,077,000 registered deaths.1 Both the GI cancer incidence and related deaths in China account for about 50% around the world, and the GI cancer burden is still increasing globally.2 Therefore, Chinese researchers have the responsibility to play a leading role in the prevention, diagnosis, and treatment of GI cancer. For advanced GI cancers, despite progress of conventional chemo-therapy, target therapy, and even immunotherapy, long-term survival of patients is still relatively low. Hence, innovation in drug research and development (R&D) is an urgent clinical need in our country, especially for the high-incidence GI cancer.

CURRENT STATUS OF ANTICANCER DRUG R&D TESTING IN GASTROINTESTINAL CANCER

In recent years, immunotherapy and targeted therapy have achieved rapid development in GI cancer. Since the approval of PD-1/PD-L1 antibodies or targeted therapeutics (e.g., bevacizumab and cetuximab) by the Food and Drug Administration or National Medical Products Administration (NMPA) for advanced GI cancers, the approval of these drugs has also inspired the development of additional new products. However, the development of innovative drugs in GI cancer, especially upper GI cancer, has much lagged compared with that in lung cancer or melanoma around the world. From 2013 until now, there have been more than 8,000 clinical trials on cancer, involving 1,347 cases in GI cancer (squamous cell carcinoma: 339; gastric cancer: 554; colorectal cancer: 428; gastrointestinal stromal tumors: 26) and 799 cases on breast cancer. Only 23 drugs have been approved, mainly in colorectal cancer, but limited drugs have been approved in esophageal and gastric cancer. In China, 70 novel first-in-class agents have been approved for treating cancer, but only five agents have been able to be used in GI cancer over the past 5 years. Moreover, the optimization of drug R&D with advanced technologies and concepts, such as utilizing artificial intelligence, antibody-dependent cell-mediated cytotoxicity (ADCC), and proteolytic targeting chimeric mechanism, has not been extensively applied in Chinese biopharmaceutical companies. Improving biopharmaceutical R&D as well as affordable cancer drugs could aid to improve the outcomes and quality of life of GI cancer patients.

Despite the increasing amount of phase I oncology trials, new molecular entities are extremely scarce in GI cancer phase I studies. However, more and more drugs based on existing molecular targets bring new opportunities and challenges for gastrointestinal tumor therapy. For example, novel HER2 directed antibody-drug conjugates, such as zanidatamab, have displayed an improved efficacy in GI cancer. For advanced GI cancers, despite progress of conventional chemotherapy, target therapy, and even immunotherapy, long-term survival of patients is still relatively low. Hence, innovation in drug research and development (R&D) is an urgent clinical need in our country, especially for the high-incidence GI cancer.

CHALLENGES OF ANTICANCER DRUG R&D DEVELOPMENT IN GASTROINTESTINAL CANCER

In preclinical research, despite the increasing number of basic studies in GI cancer, most of these bench side discoveries failed to provide any significant bedside outcomes, addressing the necessity of high-quality translational studies. A well-established translational pipeline is needed to advance each part of translational process. The ideal translational platform is equipped with preclinical patient-derived xenografts (PDX) model, immune-humanized model, and a bio-bank stor- ing blood, biopsy samples, and ascites from GI cancer patients. A series of sequencing technologies could be performed on these samples to deeply investi-gate the features of tumor microenvironment and discovery of the vulnerabilities of tumors. Notably, exploring updated methodology, such as single-cell transcript or proteomic sequencing, single-cell spatial temporal transcriptomics, and CRISPR-Cas9 system, will also improve the opportunities of promoting the R&D to clinical practice. If a specific drug showed potential anti-tumor efficacy in a preclinical model system, the phase I study could be subsequently initi-ated to test the clinical efficacy.

At the clinical level, to spur the preclinical-to-clinical translatable, first of all, within the bench side-beds-side-bench side concept, the translational studies and investigation of new drugs should be driven by the unsolved problems in clinical practice. Some clinical problems are unique for GI cancer. For example, the mechanism of peritoneal metastasis in gastric and colorectal cancer is still unclear, and how to prevent or treat the subset population with this phenotype is an important point in translational studies for GI cancer. In terms of different drug development and treatment strategy across the tumor types, the major direction for future drug research should be specific for GI cancer. Second, with the wide administration of immunotherapy in GI cancer, the acquired resistance and how to reverse this resistance deserves more attention. In addition, current promising therapeutic tar-get- s, such as MEK, KRAS, FGFR, CDK4/6, and TLR8/9, take less focus on GI cancer; how to refer to these agents and optimize the administration for GI cancer gets, such as MEK, KRAS, FGFR, CDK4/6, and TLR8/9, should be specifically studied for GI cancer research in China. Third, the real challenges for R&D drug development include the massive investments and the difficulty in precise selection of patient because of huge heterogeneity in GI cancer. These obstacles make start-up companies unwilling, and even not dare, to perform R&D drug clinical trial for GI cancer. In this situation, an R&D-type company could integrate resources and choose potential partners based on its strategy to accelerate the international clinical trial of their innovative drugs, especially for those targeting rare gene alterations seen in GI cancer.
Finally, creating a friendly environment for innovative drug discovery is also crucial to bring these molecular entities to clinics, requiring policy optimization and governmental support. Recently, in order to create a more innovation-friendly drug R&D environment, NMPA approved that medical facilities only need to register on the NMPA website to obtain approval for conducting clinical trials, shortening the complex certification step of registering a new trial. If there are no negative review assessments given within 60 working days after the application, the clinical trial is considered to be approved. Moreover, the current policy has become “tolerant entry, strict exit,” addressing the quality control of clinical trials and post-marketing pharmacovigilance. On the other hand, to spur drug innovation, NMPA has defined the innovative drugs more strictly and adopted a four-color light strategy to identify the potential novel molecular entities, which will be offered highest priority for approval. These changes facilitate Chinese biopharmaceutical companies to pay more attention to innovative drug R&D rather than generic drugs (Figure 1).

**FUTURE DIRECTIONS**

The common procedure of novel drug discovery is from initial target selection to preclinical drug exploration, followed by candidate drug selection and clinical development steps. With the expanding repertoire of the preclinical model system, the optimal model selection and accurate interpretation of data from preclinical models depend on comprehensive deciphering correlations between molecular characteristics of each model and those seen in our patients. Accessing the model translatability has been considered a crucial step during drug development, requiring characterization of the model translatability from preclinical to clinical outcomes. In this concept, it is strongly recommended that the R&D-type companies establish close cooperation with experienced clinical teams who can generate reliable samples, patient-derived models, and therapeutic cohorts.

Moreover, the biopsy samples from advanced GI cancer are usually not easily available, so these samples should be carefully stored and fully used. For example, these samples could be subjected to a “multi-omics” strategy to characterize microenvironment, uncover response and resistance mechanisms, explore therapeutic targets, and identify efficacy biomarkers. These multidimensional omics data provide rich sources for target discovery and drug development. However, how to extract accurate information and ultimately convert it into target discovery and drug development is still an open question. Ongoing, multi-institution workflows such as GENIE, DepMap, and the application of artificial intelligence to drug structure design, patient stratification, and efficacy prediction will speed up the drug development in the future.

**CONCLUSION**

Despite emerging efforts contributing to the innovative drug R&D development, the efforts paid into GI cancer are still insufficient. To further drive the innovative drug investigation in GI cancer, all stakeholders including the government, clinical investigators, scientists, and pharmaceutical companies should come together and collaborate closely. Only in this way, the R&D drug discovery in GI cancer will eventually blossom in China.

**REFERENCES**

1. Zhang, S.W., Sun, K.X., Zheng, R.S., et al. (2021). Cancer incidence and mortality in China, 2015. J. Natl. Cancer Cent. 1, 2–11. https://doi.org/10.1016/j.jncc.2020.12.001.
2. Siegel, R.L., Miller, K.D., and Jemal, A. (2020). Cancer statistics, 2020. Cancer J. Clin. 70, 7–30. https://doi.org/10.3322/caac.21590.
3. Peng, Z., Liu, T.S., Wei, J., et al. (2021). Efficacy and safety of a novel anti-HER2 therapeutic antibody RC48 in patients with HER2-overexpressing, locally advanced or metastatic gastric or gastroesophageal junction cancer: a single-arm phase II study. Cancer Commun. (Lond). 41, 1173–1182. https://doi.org/10.1002/cac.21224.
4. Sahin, U., Türeci, O., Manikhas, G., et al. (2021). FAST: a randomised phase II study of zolbetuximab (IMAB362) plus EXE versus EXE alone for first-line treatment of advanced CLDN18.2-positive gastric and gastro-oesophageal adenocarcinoma. Ann. Oncol. 32, 609–619. https://doi.org/10.1016/j.annonc.2021.02.005.
5. Qi, C., Qin, Y., Liu, D., et al. (2021). 1372O CLDN 18.2-targeted CAR-T cell therapy in patients with cancers of the digestive system. ESMO. 32, S1040. https://doi.org/10.1016/j.annonc.2021.08.1481.

**DECLARATION OF INTERESTS**

The authors declare no competing interests.