Letter

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Orphan drugs in different countries and development of new drugs to treat biliary tract cancer

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SUMMARY Biliary tract cancer (BTC), which includes cholangiocarcinoma and gallbladder carcinoma, is a rare malignancy. Due to its low incidence, drugs treating these diseases are scarce, so they can be considered orphan drugs. The main treatment choice for BTC is chemotherapy with gemcitabine or cisplatin or combined use of both, but patients fail to significantly benefit from established chemotherapy. Advancements in immunotherapy and targeted therapy will shed light on ways to improve clinical outcomes for patients with BTC. In conjunction, more new drugs will come onto the market. This article compares the conditions for development of orphan drugs in different countries and it describes several types of new drugs that were recently approved to treat BTC.

Keywords biliary tract cancer, orphan drugs, durvalumab, fibroblast growth factor receptor

Biliary tract cancer (BTC), rare but fatal, includes cholangiocarcinoma (CC) and gallbladder carcinoma (GBC). The incidence of CC is about 0.1 cases per 100,000 to 2 per 100,000 annually depending on the geographical region. The highest incidence of GBC is 27 cases per 100,000, which was observed in women in southern Chile (*1*). Due to the low incidence of BTC, there have long been few studies on corresponding drugs to treat this disease. This is because the cost of discovering those drugs cannot be recouped since so few patients have those rare diseases. Countries around the world have introduced different laws to encourage the manufacture and development of new drugs for rare diseases. The United States enacted the Orphan Drug Act in 1983. In the following years, more than 500 orphan drugs were developed. Japan's Ministry of Health has supported the development of orphan medicines since 1985. In 2000, the European Medicines Agency (EMA) enacted orphan drug regulations to encourage the development of orphan drugs. The newly amended (in August 2019) Drug Administration Law of the People's Republic of China also provides a legal basis for the treatment of rare diseases in China (*2*). One chapter of the new Drug Administration Law stipulates that the research, development, and manufacture of drugs in short supply will be encouraged and that priority will be given to the review and approval of these drugs. Despite this, there is still a gap between China and the United States in the treatment of rare diseases. Improving the system of managing orphan drugs will be the first step to narrowing that gap.

Durvalumab (MEDI4736) is a human IgG1 monoclonal antibody targeting the PD-L1 molecule. Binding by durvalumab to PD-L1 prevents the interaction between PD-1 and PD-L1, thus activating cytotoxic T cells and stimulating an immune response to tumor cells. Durvalumab was approved by the US Food and Drug Administration (FDA) to treat urothelial cancer (in 2017) and non-small cell lung cancer (NSCLC) (in 2018) (*3*). The use of durvalumab to treat urothelial cancer was based on the results of a multicenter phase I/II clinical trial (NCT01693562)(3) in which the objective response rate (ORR) was 17.8%. Results of the PACIFIC study are a well-known foundation for use of durvalumab to treat NSCLC. The PACIFIC study was a phase III clinical trial that evaluated the efficacy of durvalumab for maintenance therapy in 713 patients with locally advanced or unresectable NSCLC. Fifty-seven percent of patients receiving durvalumab lived longer than 36 months versus 43.5% of patients receiving a placebo (*4,5*). Durvalumab had a manageable safety profile in treating NSCLC, and it had no detrimental effects on patient-reported outcomes. Another randomized, controlled, open-label, phase III trial (the CASPIAN trial) evaluated the effects of durvalumab with or without tremelimumab in combination with etoposide and either

cisplatin or carboplatin (platinum–etoposide) in patients with extensive-stage small-cell lung cancer (ES-SCLC) (*6*). The CASPIAN trial noted a significantly improved overall survival (OS) in the durvalumab plus platinum–etoposide group, with more patients alive at 12 months and 18 months.

Last year, durvalumab was approved by the FDA as an orphan drug to treat BTC. Before that, a phase I study published results of combination therapy with durvalumab and tremelimumab to treat BTC. The median overall survival (mOS) of patients who received combination immunotherapy was 10.1 months, which was higher than that (8.1 months) of patients treated with durvalumab alone. In addition, promising results announced at the ASCO indicated that patients with advanced BTC who received durvalumab and tremelimumab plus chemotherapy had an mOS of 20.7 months. In addition, two ongoing clinical trials (NCT03482102 and NCT04298008) are assessing the combined administration of durvalumab and tremelimumab or AZD6738 in patients with BTC.

BPI-43487, a small molecule inhibitor of fibroblast growth factor receptor 4 (FGFR4), was approved in December 2020 for clinical use on solid tumors such as hepatocellular carcinoma and CC with upregulated expression of fibroblast growth factor 19 (FGF19). FGFRs are members of the tyrosine kinase family, and mutation or overexpression of FGFRs is found in multiple types of cancer. An inhibitor of FGFR1-3, infigratinib, was also approved for clinical research on treatment of advanced solid tumors including BTC, gastric cancer or adenocarcinoma of the gastroesophageal junction, and other tumors with FGFR mutations. Moreover, clinical trials on FGFR inhibitors such as TAS-120, derazantinib, and erdafitinib for treatment of CC have already yielded encouraging outcomes. A point worth noting is that erdafitinib is the world's first FGFR-targeting drug to be approved. FGFRs have become a hot topic of research. In 2020, pemigatinib, the second FGFR inhibitor that came onto the market, received accelerated approval for treatment of advanced BTC (*7*). The approval of pemigatinib was based on the FIGHT-202 study, which suggested that patients with CC and an FGFR2 fusion gene obtained a considerable benefit from targeted therapy. The mOS of patients receiving pemigatinib was 21.1 months, which was significantly higher than that of other groups (*8,9*). In addition, ongoing clinical trials based on FGFR targeting are also focused on lung cancer, hepatoma, breast cancer, and other types of cancer. In the future, FGFRs could serve as a target for therapies to treat a large variety of tumors.

In recent years, immunotherapy and targeted therapy have achieved remarkable success in the treatment of solid tumors. Increasing numbers of monoclonal drugs and targeted drugs have been approved for clinical use. With support from the government and the great promise of these drugs, increasing numbers of clinical trials are focusing on use of those drug to treat BTC. There are high hopes for improved clinical outcomes as a result of new drug development.

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