

Overview of Gastrointestinal Tumors and Therapeutic Advances in East Asia

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Abstract. In East Asia, gastrointestinal tumors are a common group of malignant tumors, including gastric, colorectal, and liver cancers. The high incidence of gastrointestinal tumor neoplasms is related to various factors, including genetic factors, dietary habits, environmental factors, and infections (e.g., *Helicobacter pylori* infection). In recent years, monoclonal antibody therapeutic modalities targeting HER2, PD-L1, and EGFR have been proved to have unique effects in treating gastrointestinal tumors, providing a new direction for treatment. HER2, a protein overexpressed in some certain populations, has been linked to the occurrence, growth and metastasis of the tumor. Related experiment results proved monoclonal antibody therapy targeting HER2 (e.g., trastuzumab) has shown to significantly improve the efficiency of treating gastrointestinal tumors. PD-L1 is a surface of tumor cells protein which helps tumors to evade attack by the immune system. Treatment with PD-L1 monoclonal antibody therapy, such as pembrolizumab and nivolumab, has shown benefits in enhancing the immune system's capacity to recognize and eradicate tumors. Aberrant activation of EGFR act as an important role in the growth of enormous gastrointestinal tumors. Monoclonal antibody treatments directed against EGFR, such as cetuximab, can efficiently disrupt the EGFR signaling cascade, thus suppressing the proliferation and viability of cells in tumor. Meanwhile these monoclonal antibody therapies can be used not only alone, but also in combination with chemotherapy, targeted therapeutic agents to enhance the effectiveness of treatment. For example, dual targeting of HER2 and PD-L1 has shown enhanced efficacy in clinical trials. In addition, the combination of monotherapy targeting EGFR with KRAS G12C inhibitors has shown promise in colorectal cancer treatment. In summary, the three monoclonal antibody therapeutic modalities of HER2, PD-L1, and EGFR have unique advantages in the treatment of gastrointestinal tumors, which not only provide precise therapeutic approaches against different molecular targets, but also open up new paths for the development of combination therapeutic strategies. With future research, these treatments are expected to further improve the recovery rate and the life quality of people with gastrointestinal tumors.

Keywords: Gastrointestinal Tumors Monoclonal Antibody Therapy Therapeutic Advances.

1. Introduction

The efficacy of treatment for gastrointestinal tumors is related to a number of factors, such as the areas of tumor distribution in the body, which has an impact on the outcome of treatment, and as cardia involvement increases, the survival of patients with such involvement decreases after developing gastrointestinal tumors. In addition, compared with anterior involvement, atrial involvement leads not only to an increased likelihood of mortality as well as an increased likelihood of the condition reoccurring. Thus, atrial involvement decreases the likelihood of mortality, whether recurrence occurs or not [1]. Also, the success rate of gastrointestinal tumors is gradually increasing with the continuous progress of treatment technology. With the improvement of surgical techniques and anesthesia methods, the gradual expansion of surgical scope as well as the gradual improvement of surgical techniques, surgical treatment has been gradually applied to a wider range of tumor stages and types, and has become one of the main methods of treating gastrointestinal tumors. In the middle of the twentieth century, with the emergence of chemotherapeutic agents, such as fluorouracil, the therapeutic outcome of gastrointestinal tumors was significantly improved. Since the 1990s, the increased precision and efficacy of radiation therapy, including the application of techniques like ionizing radiation therapy and three-dimensional conformal radiation therapy, have made radiation

therapy another important tool in treating gastrointestinal tumors [2]. Different treatment modalities for gastrointestinal tumors have shown unique advantages in different contexts. In the study of Smith et al. showed surgery itself has achieved good efficacy in early gastrointestinal tumors however in advanced patients' surgery often needs to be combined with other therapies such as chemotherapy to demonstrate better efficacy [3]. In recent years monoclonal antibodies that specifically bind to tumor cell surface, bringing a new dawn for patients with gastrointestinal tumors. By specifically targeting biomarkers on the surface of cells in tumors, monoclonal antibodies alleviate the adverse reactions of patients during treatment by promoting CD8+ T cell recruitment and natural killer cytotoxicity to enhance the host's anti-tumor immunity, among other things, as opposed to single surgical treatment as well as chemotherapy [4]. The aim of this paper is to provide an overview of the epidemiological characteristics of gastrointestinal tumors in East Asia, factors of malignancy, and several monoclonal antibody treatment modalities, mainly HER2 PDL-1 EGFR, with a focus on the unique advantages of monoclonal therapy in treating gastrointestinal tumors.

2. Principles of Gastrointestinal Tumor Treatment

2.1. The Incidence Patterns of Gastrointestinal Tumors in East Asia

Liver cancer has the most elevated mortality rate among these, with gastric, colorectal, esophageal, pancreatic, and gallbladder cancers closely following in terms of mortality. Globally, gastrointestinal tumors account for more than 25% of all tumor incidence and 35% of tumor-related mortality. The prognosis of colorectal cancer has improved considerably through early screening, but other types of gastrointestinal tumors are mostly diagnosed at a more advanced stage with a poor prognosis [3]. From the perspective of overall incidence and overall mortality, the overall incidence (85.7/100,000) and mortality (59.8/100,000) of gastrointestinal tumors in East Asia are higher than those in Europe (55.5/100,000) and (32.5/100,000), Oceania (52.4/100,000) and (25.5/100,000), and North America (48.7/100,000) and (23.9 /100,000). Meanwhile, in 2020, East Asia recorded 2,488,742 newly diagnosed cases of gastrointestinal tumors, representing 48.4% of the worldwide incidence figure. Specifically, the age-standardized incidence rate of gastrointestinal tumors in East Asia is 85.7/100,000, with Mongolia (146.1/100,000) having the highest rate, followed closely by Japan (995,000/100,000), China (83.0/100,000), South Korea (819,000/100,000), and North Korea (59.9/100,000). Regarding mortality, East Asia documented 1,778,161 fatalities attributed to gastrointestinal cancers in 2020, constituting 49.0% of global deaths from gastrointestinal cancer. With a mortality rate of 130.1/100,000, Mongolia has the highest rate in East Asia, followed by China (63.8/100,000), Korea (475/100,000), Japan (363/100,000), and North Korea (32.8/100,000). It can be concluded that gastrointestinal tumors in East Asia are higher in terms of incidence and mortality compared to other regions of the world. According to gender division, taking the global incidence of colorectal cancer in 2017 as an example, male age-standardized incidence rates were higher than those of females in all regions except Latin America, and mortality rates were similarly higher when comparing with those of women in all regions [4]. In terms of subtype, the occurrence rates of colorectal and pancreatic cancers are less prevalent in East Asia compared to Europe, Oceania, and North America. However, stomach, liver, esophagus, and gallbladder cancers have an even heavier burden in East Asia, and the prevalence of colorectal and pancreatic caners is increasing, with forecasts indicating a 58% surge in new cases and a 73% rise in fatalities, respectively, by 2040 [4]. Thus, gastrointestinal tumors are a huge disease burden in East Asia, and the incidence and mortality rates vary by gender and subtype. Among the factors causing gastrointestinal tumors, in East Asia, *Helicobacter pylori* (HP) infection is also regarded as a significant factor contributing to gastric cancer, and according to a collaborative study from the University of Oxford, and other research centers, *H. pylori* is one of the major infectious agents in gastric carcinogenesis, elevating the risk of non-cardia gastric cancer by a factor of six and cardia gastric cancer by a factor of three [5]. This study included data on 512,715 adult patients used a case-cohort study design after ten years of follow-up, which showed that 78.5% of non-cardia cancers and 62.1% of cardia cancers were related

to *Helicobacter pylori* (HP) infection. Accordingly, it was estimated that about 339,955 new cases of gastric cancer were attributed to HP infection. In addition, Chinese branch testicular schistosomiasis, which is widely prevalent in East Asia, especially in Guangdong, Guangxi and Heilongjiang regions of China, is considered to be a unique predisposing factor leading to cholangiocarcinoma, hepatocellular carcinoma and gallbladder cancer. A study published in PLOS Neglected Tropical Diseases provides evidence for this by demonstrating an association between *S. cerevisiae* infection and hepatocellular carcinoma. This study demonstrated that infections of *S. cerevisiae* were correlated with a range of damages to the hepatobiliary system, such as inflammation, cholangiocarcinoma, and hepatocellular carcinoma. There was also a significant clinicopathologic association between *H. pylori* infection and hepatocellular carcinoma, including gender, BCLC stage, cirrhosis, and specific marker factors such as AFP and CA19-9. HC infection enhances the development of cancer stem cell-like traits in hepatocellular carcinoma and speeds up the advancement of malignancy [6]. Viral hepatitis is also a significant contributing factor to liver cancer prevalence in East Asia. Statistics indicate that over 250 million individuals globally carry the HBV virus, with countries in Asia and Africa, where infections exceed 8%, accounting for approximately 70% of all infections. The annual incidence of HCC in patients with cirrhosis due to chronic HBV or HCV infection is 2%-5%. HBV/HCV co-infection significantly increased the likelihood of cirrhosis and HCC compared to infection with either virus alone. In addition, chronic HBV or HCV infection increases the risk of HCC several-fold and progression from HBV to HCC involves complex interactions, which are vital in hepatocellular carcinoma progression. A study concluded that consumption of beverages at temperatures above 65°C significantly elevated the likelihood of developing esophageal squamous cell carcinoma. Studies have shown that individuals who smoke face an increased risk of gastric and colorectal cancers, and Buttery et al.'s study showed a Significantly associated [7] therefore regular consumption of hot drinks, smoking and alcohol intake are also considered to be important risk factors contributing to the incidence of malignant tumors.

2.2. Factors Trigger Gastrointestinal Tumors

Under normal physiological conditions, oncogenes participate in controlling cell proliferation and viability, and when mutations occur, oncogenes may become over-activated, which triggers uncontrolled cell proliferation and eventually leads to tumor formation. For example, Mutations in the RAS gene family are common in many types of tumors, leading to sustained activation of cell proliferation signaling pathways [8]. Tumor suppressor genes help to control normal cell division, thus maintaining genomic stability. When tumor suppressor genes are inactivated by mutations, the regulation of normal cell division is imbalanced, leading to carcinogenesis Cells usually have mechanisms for DNA repair damage. For example, TP53 is one of the most common oncogenes, and mutations lead to the development of a variety of tumors [9]. In addition, DNA repair genes are responsible for repairing DNA damage and maintaining genome stability. Alterations in these genes can result in the buildup of DNA damage, consequently heightening the likelihood of carcinogenesis. When the above mechanisms are impaired due to mutations, DNA damage accumulates and further promotes tumor development. For example, malfunctions in the mismatch repair system (MMR) are connected to Lynch syndrome, a hereditary condition linked to colorectal cancer without multiple polyps, and people with a family history of Lynch syndrome have an increased risk of colorectal cancer due to mutations in the MMR gene. Also, individual background has a significant effect on the risk of gastrointestinal tumors, such as dietary habits, smoking, alcohol consumption, and persistent infections are linked to a higher likelihood of gastrointestinal tumors and facilitate the process of tumorigenesis. For example, reactive oxygen species and pro-inflammatory cytokines produced under inflammatory conditions in patients with chronic ulcerative colitis led to DNA damage, promote cellular gene mutations, and ultimately lead to cancer [10].

3. Monoclonal Therapy in Gastrointestinal Tumors

Monoclonal antibodies therapy has attracted much attention in recent years as an emerging trend in gastrointestinal tumor therapy for their unique therapeutic mechanisms such as the ability to target specific molecular targets. It has shown remarkable effects in regulating immune response, inhibiting tumor growth and metastasis, and has become an important means to improve patients' survival quality and prolong survival time. This article focuses on the HER2 PDL-1 and EGFR mechanisms of monoclonal antibody therapy for gastrointestinal tumors.

3.1. HER2

In gastrointestinal tumors, tumor aggressiveness, metastatic ability and patient prognosis strongly associates with over expression of HER2. Specifically, in gastric cancer, the overabundance of HER2 is a significant predictor of outcomes and a crucial focus for precision-targeted treatments. Approximately 12%-18% of gastric cancer cases show overexpression or gene amplification of HER2, which is linked to a more severe form of the disease, reduced response to therapy, and decreased overall survival. In contrast, HER2's involvement in colorectal cancer (CRC) is multifaceted, and the proportion of HER2 overexpression in CRC is low, but in some subtypes, such as metastatic CRC with KRAS wild-type, HER2 may be a potential therapeutic target [11]. Currently, treatment for HER2 targets mainly relies in identifying HER2 amplification or overexpression, and HER2 expression detection methods, in particular, is closely correlated with aggressive disease, which assessed using immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH). Usually, IHC and FIS can be used as independent assays, but when two of them are ineffective to be used independently at the same time both can be used at the same time for detection. According to the NCCN guidelines [12], individuals diagnosed with stomach cancer should be treated with HER2 testing when they are in locally advanced, recurrent, or metastatic disease that cannot be treated surgically, and one of the preferred methods is IHC/ISH. For patients with limited diagnostic tissues or inability to undergo conventional biopsy, second-generation sequencing (NGS) can be an optional complementary test after IHC/ISH testing, or can be considered as an Alternative option for ISH. In 2010, the ToGA [13] study, for the initial time, revealed that the pairing of trastuzumab with chemotherapy extended patient survival, thus opening the era of anti-HER2 targeted therapy in gastric cancer. However, subsequent cross-line and high-dose studies of other HER2-targeted agents, including lapatinib, T-DM1, patuzumab, and trastuzumab, ended in failure. In the last decade or so, treatment options beyond the first line for HER2-positive gastric cancer have been restricted, and patients' treatment options and survival benefits have been restricted, hence, there is an urgent necessity to explore innovative treatment strategies. In East Asia, recent clinical trials and studies have customized HER2-targeted therapies based on regional genetic variants and treatment response, such as a study by Kim [14] et al. showing the effectiveness of new HER2-targeted treatments in a group of East Asian patients with gastric cancer. Meanwhile, the latest generation ADC drug T-DXd, which plays a role in killing tumor cells globally, selectively binds antigens of target cells through the targeting effect of antibodies to form ADC-antigen complexes, enters into tumor cells through endocytosis and releases cytotoxic carriers through the cleavage of the linker by the action of lysosomes, while the cleavage of the cleavable tetrapeptide-based linker that combines the anti-HER2 monoclonal antibody T-DXd with topofloxacin, the latest generation ADC drug, plays a role in killing tumor cells. Trastuzumab was utilized in conjunction with the topoisomerase I inhibitor DXd [15]. After internalization of HER2 by HER2-expressing cells, the T-DXd linker breaks to release the highly membrane permeable DXd, which can exert its potent cytotoxic effect on adjacent tumor cells through bystander effect while killing the target tumor cells, thus overcoming the strong heterogeneity of gastric cancer tumor cells and enhancing the efficacy [16]. In addition, the cytotoxic load of T-DXd, DXd, is a type of topoisomerase I inhibitor that offers the benefit of circumventing cross-resistance by a different mechanism than the platinum and fluorouracil chemotherapeutic agents commonly utilized as a primary treatment option in gastric cancer. A study at the European Society of Clinical Oncology in 2023 explored Pembrolizumab (pembro) combined with trastuzumab and

chemotherapy is suggested as an initial treatment option for patients diagnosed with HER2-positive metastatic gastric cancer or gastroesophageal-joint (mG/GEJ) adenocarcinomas [17], with a major breakthrough. Namely, in the KEYNOTE-811 phase III study, the pembro combination therapy showed significant efficacy improvement compared to the placebo group (pbo) using only trastuzumab and chemotherapy. The study had a design was employed that involved randomization, double-blinding, and a placebo-controlled approach, in which patients, including the untreated, unresectable HER2-positive mG/GEJ adenocarcinoma population, were randomly assigned to receive either pembrolizumab or standard chemotherapy and trastuzumab as part of the standard of care. With Progression-free survival and overall survival, the main focus of the study as primary endpoints, treatment was continued for a maximum of 2 years or until disease progression or intolerable toxicity. As data cut off on May 25, 2022, total patients randomly assigned, the conclusive findings of the study demonstrated a notable enhancement in the rate of surviving of free progression within the pembro + SOC group compared to the pbo + SOC group, with a median PFS of 10.0 months versus 8.1 months (HR 0.72), Particularly among patients with PD-L1 CPS ≥ 1 , there was a significant improvement in median PFS, with 10.8 months observed in the pembro + SOC group compared to 7.2 months in the pbo + SOC group. Furthermore, the pembro group exhibited higher objective response rates (ORR) and longer durations of remission (DOR) compared to the placebo group. The incidence of grade ≥ 3 drug-related adverse events (AEs) was 58% and 51% in the two groups, showing acceptable tolerability. In the case of individuals diagnosed with HER2-positive metastatic or locally advanced gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma increased objective response rate (ORR), and had a longer duration of remission (DOR) compared to the conventional placebo combination of trastuzumab and chemotherapy regimen. An acceptable safety profile was also maintained.

3.2. PD-L1

Within the tumor microenvironment of the gastrointestinal tract, the most important way PD-L1 functions or operates in tumors are the increased expression of PD-L1 which directly interacts with PD-1 on the surface of T cells, resulting in the suppression of T cell activity, thereby facilitating the proliferation and dissemination of cancerous cells. Meanwhile, PD-L1 can also influence additional immune cells within the tumor's surrounding environment, such as suppressing the development and stimulation of dendritic cells, diminishing the generation of immune-stimulating substances, and enhancing the manifestation of immune-suppressing factors. Besides the PD-1/PD-L1 axis, PD-L1 may interact with other immune checkpoint molecules to jointly participate in the control of the immune reaction, and the complex network of interactions formed increases the possibility of immune escape [18]. Currently, benefits are brought through PD-1/PD-L1 blockade therapy in numerous types of cancers, however, cells in tumors themselves can evade the immune response and evolve to counteract PD-1/PD-L1 blockade treatment, laying the groundwork for PD-1/PD-L1 blockade therapy to provide sustained benefits to patients. Clinical practice has shown that even when acting on patients with highly PD-L1-sensitive tumors, more than 50% of patients don't show response to PD-1/PD-L1 inhibitor treatment. Meanwhile, treated with PD-1/PD-L1 blockade treatment in micro satellite unstable cancer of the colon or rectum (MSI-H CRC), the rate of surviving is only 30%~50% among patients, meaning that some patients may still experience disease re-progression even after their tumors have been controlled, i.e., there is a resistance problem to PD-1/PD-L1 blockade therapy. Currently, relevant research believes that only patients with MMR-deficient/microsatellite unstable colorectal cancer (dMMR/MSI-H type mCRC) can gain advantage from PD-1/PD-L1 blockade therapy, but certain individuals still develop drug resistance after receiving PD-1/PD-L1 blockade treatment sometimes. As a reaction to drug resistance in patients, experts and scholars are actively exploring ways to destroy tumors in various fields, including chemotherapy, radiotherapy, and targeted therapy, and are committed to the direct strategy of immunotherapy in combination with other therapeutic tools i.e., releasing tumor antigens during treatment. Encouragingly, immunotherapy in combination with other therapies has not weakened the immune response as in the

past, but rather enhanced it. Therefore, some scholars have begun to study the combined application of immunotherapy with radiation therapy, chemotherapy, and precision therapy, and even try to utilize a blend of two immunosuppressive medications in order to reduce immunotherapy resistance, improve therapeutic efficacy, and prolong the survival time of patients. Combination chemotherapy proved to be a feasible approach, and conventional chemotherapy increases the immunogenicity of tumor cells by inducing immunogenic cell death (ICD), which reverses immune resistance. In addition, myeloid-derived suppressor cells (MDSCs) are able to evade the cellular self-defense system through accelerating the growth and capability of CD8⁺ T cells. Classical chemotherapeutic agents such as 5-fluorouracil have been found to induce apoptosis in MDSCs and enhance T cell-mediated antitumor responses [19]. For example, Pembrolizumab is an anti-PD-1 drug employed for the therapy of dMMR/MSI-H subtype of metastatic colorectal cancer (mCRC). Despite its better efficacy, its further clinical application is constrained by the issues of toxic adverse reactions and drug resistance present in the drugs. Therefore, some scholars have proposed combination therapy with chemotherapeutic agents. Traditional chemotherapy drugs like 5-fluorouracil and oxaliplatin are thought to have the impact of improving the function of the patient's immune system by promoting the expression of tumor antigens. For instance, Limagne have conducted a study in 2016 involving 25 individuals diagnosed with metastatic colon cancer, all of whom received treatment comprising a FOLFOX chemotherapy protocol combined with a medication that inhibits PD-1/PD-L1. The research results indicated a decrease in regulatory T cells (Treg) observed in blood samples from 15 patients, accompanied by a significant increase in myeloid-derived suppressor cells (MDSC) and pro-inflammatory Th17 helper T cells, suggesting that the FOLFOX chemotherapy regimen It may have a potent inhibitory effect on the PD-1/PD-L1 pathway and enhance the effects of PD-1/PD-L1 inhibitors [20]. Another study evaluated 30 patients with inoperable colorectal cancer who received treatment with a PD-1/PD-L1 inhibitor alongside oxaliplatin-fluorouracil-calcium folinic acid regimen (mFOLFOX6 regimen), which showed that the disease stabilization rate of the patients was the complete remission rate was 100% after about two months, and the overarching remission rate stood more than 50% after about 6 months [21]. Combination targeted therapy is another viable approach. Zelenay et al. showed [22] that anti-vascular endothelial growth factor (VEGF) treatment combined with immunotherapy can improve the immunosuppressive state of the body. VEGF inhibitors boost the growth and activity of cytotoxic T lymphocytes, stimulate effector T cells repeatedly, and inhibit the aggregation of T-regulatory cells (Tregs). In addition, by normalizing the vascular endothelium within the tumor, anti-VEGF drugs can increase the extent of tumor infiltration by CD8⁺ T cells and improve sensitivity to PD-1 blockade therapy. Recent studies have shown that combining regorafenib, a tiny chemical compound tyrosine kinase inhibitor (TKI), with Nivolumab in patients with rectal cancer achieved promising results. Regorafenib is not only a potent antiangiogenic drug, but also an inhibitor of tumor-associated kinases, which can block VEGF receptors and reduce the number of immunosuppressive cells like macrophages found within tumors. Thus, regorafenib could theoretically exert antitumor effects in synergy with PD-1/PD-L1. A study evaluating Nivolumab Demonstrated when using alongside regorafenib for treating patients with advanced or metastatic colorectal and gastric cancers that 25 of these colorectal cancer patients had an ORR of 36%, and eight achieved objective remission. The average duration of progression-free survival for colorectal cancer patients was 7.9 months. In addition, the combined treatment of regorafenib and Nivolumab exhibits a favorable safety characteristic with fewer adverse effects and can be effectively managed. Meanwhile, in the human immune system, in lymph and tissues, the CTLA-4 pathway leads to tumor cell immune escape by down-regulating the level of T-cell activation and inhibiting dendritic cell activation; therefore, blocking CTLA-4 signaling increases T-cell diversity and facilitates antigen presentation, as well as promotes T-cell infiltration and remodeling of the immune memory, and is not cross-resistant to PD-1 antibodies. Combination immunotherapy with this experimental principle can block these two pathways at the same time, which can theoretically exert synergistic effects and enhance anti-tumor effects [23]. Multiple therapeutic

strategies such as combination chemotherapy, radiotherapy, and targeted therapies are one of the approaches to tackle resistance to treatment involving the blocking of PD-1/PD-L1 interaction.

3.3. EGFR

EGFR, a receptor tyrosine kinase located on the cell membrane, is widely present in both human epidermal and stromal cells. Activation of EGFR promotes cell growth and differentiation, including embryonic development, maintenance and repair of adult tissues, and its overexpression or activation is strongly linked to the advancement and worsening of various types of cancers. In gastrointestinal tumors, aberrant activation of EGFR can stimulate the proliferation, invasion, and spread of tumor cells via numerous pathways. The EGFR signaling cascade comprises crucial pathways like RAS, which are involved in controlling cell viability, growth, and programmed cell death. Therapeutic strategies against EGFR include two main classes: small molecule tyrosine kinase inhibitors (TKIs) and monoclonal antibodies. Tyrosine kinase inhibitors (TKIs) like gefitinib and erlotinib obstruct the kinase function of EGFR, thus hindering the initiation of downstream signaling pathways. In contrast, monoclonal antibodies like cetuximab and panitumumab impede EGFR signaling by attaching to the extracellular structural domains of EGFR, preventing its interaction with natural ligands [24]. Cetuximab, as a monoclonal antibody, can precisely inhibit the function of EGFR, thus preventing the proliferation and spread of gastric cancer cells. And Panitumumab is a tyrosine kinase inhibitor, which can inhibit the triggering of EGFR signaling pathway, thus reducing the growth and metastasis of gastric cancer cells. Compared with traditional chemotherapeutic drugs, EGFR-targeted drugs have several advantages. First, EGFR-targeting drugs can target EGFR specifically expressed by cancer cells while avoiding affecting the development and specialization of healthy tissues and cells, thus reducing side effects. Second, EGFR-targeting drugs can inhibit the functioning of the EGFR signaling cascade, thus inhibiting the growth and spread of cancerous cells. Finally, EGFR-targeted drugs are usually better tolerated than conventional chemotherapeutic agents because their tumor-specific effects do not affect the growth of healthy tissues. EGFR-targeted drugs work primarily by interfering with the activation of the EGFR signaling pathway [25]. When EGFR binds to its ligands, it will trigger its subsequent signaling pathways, including ras-raf-mek-erk, STAT, and many other signaling pathways, which will then promote cell proliferation, growth, angiogenesis, and metastasis. EGFR targeting drugs inhibit the auto-phosphorylation of EGFR i.e., binding to EGFR's Tyrosine kinase binding, preventing the binding of EGFR to its ligand and inhibiting the autophosphorylation of EGFR. Meanwhile EGFR can inhibit downstream signaling pathways. For example, the initiation of the ras-raf-mek-erk pathway for signaling can be inhibited, thereby hindering the growth and spread of cancerous cells. In addition, EGFR-targeted drugs can also induce apoptosis, by regulating the expression of genes such as the Bcl-2 family and p53, which induces apoptosis and thus promotes tumor cell death [26]. In East Asia, EGFR exon 19 deletion and L858R point mutation are common types of EGFR mutations in gastrointestinal tumors. These mutations make tumor cells very sensitive to EGFR-targeted drugs, making EGFR-targeted therapy particularly important for patients with EGFR mutation-positive gastrointestinal tumors. In a study at the European Society of Oncology 2023 [17], The research presented findings from a Phase III trial of CodeBreak 300, and assessed how effective sotolacib combined with panitumumab is compared to the standard treatment in patients with chemotherapy-resistant metastatic colorectal cancer characterized by the KRAS G12C mutation. In this global open-label study, 160 patients were allocated into three groups randomly, with each group receiving one of the following treatments: sotolacib at a dose of 960 mg along with panitumumab at a daily dose of 6 mg/kg, sotolacib at a daily dose of 240 mg combined with panitumumab at a dose of 6 mg/kg, or the choice of TAS-102 or regorafenib as decided by the investigator. The main findings showed that progression-free survival was significantly better in the two groups of patients treated with sotolacib + panitumumab than in the group receiving standard therapy: the hazard ratio in the sotolacib 960 mg + panitumumab group was 0.49 (95% CI: 0.30, 0.80; $p=0.006$), and in the sotolacib 240 mg + panitumumab group, the HR was 0.58 (95% CI: 0.36, 0.93; $p=0.03$). The benefits of the combination in delaying disease progression were demonstrated based

on the above data. Regarding safety, in patients receiving sotolacib at 960 mg along with panitumumab, grade ≥ 3 treatment-related adverse events included acne-like dermatitis (11.3%), hypomagnesemia (5.7%), and rash (5.7%). In the group receiving sotolacib at 240 mg with panitumumab, the most common grade ≥ 3 TRAEs were hypomagnesemia (7.5%) and diarrhea (5.7%). Conversely, in the standard treatment group, the most prevalent treatment-related adverse events (TRAEs) were neutropenia (23.5%), anemia (5.9%), and hypertension (5.9%). In individuals with metastatic colorectal cancer (mCRC) that is resistant to chemotherapy and harbors the KRAS G12C mutation, treatment with sotolacib in combination with panitumumab was significantly superior to standard therapy in terms of progression-free survival, while offering an acceptable safety profile. This marks the inaugural phase 3 trial conducted for this specific tumor type, offering crucial insights for guiding future treatment approaches.

4. Conclusion

In East Asia, although the disease burden of gastrointestinal tumors remains high, the treatment of gastrointestinal tumors is witnessing breakthroughs and significantly improving patient prognosis with the increasing insights into their pathogenesis and the development of monoclonal antibody therapeutic technologies with key therapeutic targets such as HER2, PD-L1 and EGFR. Currently, investigating the factors contributing to drug resistance is crucial to accelerate the improvement of survival outcomes and the development of better treatment regimens for patients with colorectal cancer. Combined with other therapeutic methods, such as radiotherapy, chemotherapy, targeted or even two immune-blocking drugs, it may reduce immunotherapy resistance, improve therapeutic efficacy and prolong the survival time of patients. However, at the same time, it is inevitable to face the superimposed toxic effects brought by combination therapy. Looking ahead, therefore, future research endeavors will require collaborative efforts between fundamental researchers and clinical practitioners to tackle resistance issues in PD-1/PD-L1 blockade therapy for colorectal cancer immunotherapy. In addition, the application of advanced genomic and proteomic technologies is expected to uncover new therapeutic targets and enable more precise patient triage and treatment. At the same time, ongoing clinical trials will deepen the understanding of HER2, PD-L1, and EGFR therapy, facilitate the optimization of treatment regimens, and stimulate the advancement of novel therapeutic approaches. More studies will explore these therapeutic modalities in different subtypes of tumors and explore the combination with other therapies. The resolution of the resistance mechanism and its overcoming will also become the focus to enhance the therapeutic effect and bring more effective, safe and personalized therapeutic regimens to patients, greatly improving the rate of survival and overall quality of life.

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