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THE RELATIONSHIP BETWEEN IMMUNE CHECKPOINT INHIBITORS IN COLORECTAL CANCER

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Abstract: In the past decade, colorectal cancer immunotherapy has made great progress, especially for mismatch repair-deficient (dMMR)/microsatellite instability-high (MSI-H) colorectal cancer phenotypes, immunotherapy has sustained therapeutic responses, and achieved significant clinical efficacy. However, most metastatic colorectal cancers are non-mismatch repair deficient (pMMR) or microsatellite stable (MSS), and these patients benefit less from immune checkpoint inhibitors (ICIs). With the widespread development of clinical trials of ICIs in colorectal cancer, immunotherapy has gradually expanded its indications due to its proven efficacy, and has become the standard first-line treatment for patients with dMMR/MSI-H advanced colorectal cancer. For patients with pMMR/MSS, ICIs have also shown potential therapeutic effects by combining chemotherapy and targeted therapy. This article mainly discusses the application of ICIs in colorectal cancer, analyzes the relationship between tumors and the immune system, and outlines the immunological characteristics and classification of colorectal cancer as well as the latest progress of ICIs in the treatment of colorectal cancer.
Keywords: Colorectal tumors; Immune checkpoint inhibitors; Immunity therapy; Biomarkers

1 HISTORY OF IMMUNOTHERAPY FOR CRC

Colorectal cancer (CRC) is one of the most common malignant tumors, with high morbidity and mortality [1]. Immune checkpoint inhibitors (ICIs) are one of the most promising immunotherapy methods. They have been approved by the U.S. Food and Drug Administration (FDA) and can be used to treat different types of advanced cancer. Malignant tumors such as melanoma and non-small cell lung cancer. Anti-cytotoxic T-lymphocyte -associated antigen 4 (CTLA-4) antibodies were among the first to be tested clinically, and Ipilimumab was the first ICIs approved for anti-cancer treatment. Targeting programmed cell death receptor 1 1, PD-1) or one of its ligands, programmed cell death-ligand 1 (PD-L1), is being actively developed for use in a variety of cancers, including advanced melanoma and lung cancer. Based on these encouraging results, multiple immunotherapy clinical trials in CRC patients are also ongoing. This article will introduce in detail the latest clinical progress in CRC immunotherapy and the mechanism of action of ICIs, and discuss the use of ICIs to treat deficient mismatch repair (deficient). mismatch repair (dMMR)/microsatellite instability-high (MSI-H) CRC and non-mismatch repair-deficient (mismatchrepair-proficient (pMMR))/microsatellite stable (MSS) patients. And describes its adverse effects compared with chemotherapy alone.

Based on the results of multiple clinical studies of ICIs in CRC, the treatment strategy for advanced CRC has been gradually changed. Based on the results of the KEYNOTE-164 study [2], the FDA approved KEYTRUDA (Pembrolizumab) on May 23, 2017 for the late-line treatment of dMMR/MSI-H pan-solid tumors [3], which has since opened the door to Chapter on immunotherapy for advanced CRC. In July 2017 and July 2018, based on the results of the CheckMate-142 study [4], the FDA approved nivolumab (O drug) as a single agent and in combination with the low-dose CTLA-4 inhibitor ipilimumab, respectively. (YERVOY, Y drug) for late-line treatment of dMMR/ MSI-H CRC patients [5-6]. With the phase III randomized clinical trial KEYNOTE- The results of Study 177 [7] were announced. The immunotherapy group was more effective than the standard regimen of chemotherapy combined with targeted therapy in the control group. In June 2020, the FDA approved pembrolizumab alone for the treatment of unresectable or metastatic dMMR/MSI-H. As the first-line treatment for patients with colorectal cancer [8], immunotherapy has since achieved a leap from late-line to first-line treatment. At the American Society of Clinical Oncology of Clinical Oncology (ASCO)) 2021 Annual Meeting, KEYNOTE -177 The study announced the final overall survival (OS) results [9]. Soon on June 11, 2021, China's National Medical Products Administration Products Administration (NMPA) approved pembrolizumab for the first-line treatment of patients with unresectable or metastatic dMMR/MSI-H CRC in China, becoming another new biomarker-guided precision PD-1 treatment approved in China.

2 BASIC PRINCIPLES OF CRC IMMUNOTHERAPY

ICIs are a specific type of immunotherapy that target co-inhibitory receptors on T cells, such as CTLA-4 and PD-1, or their ligands, such as PD-L1 on tumor cells and various immune cells. to enhance anti-tumor immune responses. Under normal circumstances, T cell receptors (TCR) react on homologous antigen peptides of antigen-presenting cells (APCs) and major histocompatibility complex (MHC) class I molecules. After recognition, CTLA-4 is immediately up-regulated, and its expression reaches its peak 2 to 3 days after activation [10]. CTLA-4 inhibits TCR signaling by competing with the costimulatory molecule T cell receptor CD28 for CD80 and CD86, and CTLA-4 has a higher affinity [11]. The main function of CTLA-4 is to regulate T cell activity at T cell priming sites (such as secondary lymphoid organs), which has

been fully demonstrated in CTLA-4 knockout mice [12]. Regulatory T cells (Tregs) can also inhibit anti-tumor immunity through CTLA-4 [13]. Studies [14] have shown that specific deletion of CTLA-4 in Tregs is sufficient to induce abnormal activation of T cells and cause autoimmunity. ICIs can prevent T cell dysfunction and apoptosis, enhance T cell activation, and enhance the cytotoxic killing effect on tumor cells. PD-1 is expressed on the surface of immune cells, and PD-L1 is distributed as a ligand on the surface of tumor cells. The surface of solid tumor-invasive lymphocytes shows PD-1 positivity. The combination of PD-1 and PD-L1 inhibits T cell function and induces tumor cell immunity. escape. Blocking the combination of PD-1 and PD-L1 can prevent immune escape of tumor cells and promote T cell-mediated killing of cancer cells [15].

3 dMMR/MSI-H AND pMMR/MSI-L CLASSIFICATION OF CRC

Tumor mutational burden (TMB) refers to the total number of somatic gene coding errors, base substitutions, gene insertion or deletion errors detected per million base pairs [16]. Loss of expression of any MMR protein can cause dMMR, which causes the loss of repair function of base mismatches during DNA replication, resulting in the accumulation of TMB, leading to the occurrence of MSI. CRC According to their mutation patterns, they can be divided into two types: tumors with high mutation burden (about 10%) with dMMR/MSI-H characteristics and pMMR/MSI-L Characteristic low mutation load tumors (accounting for about 90%) [17]. Correlation between mutation incidence and immunotherapy response suggests that tumor cells with high mutational burden More peptide neoantigens are produced and presented on class I molecules. Therefore, these tumors are more likely to be recognized as non-self, thereby triggering T cell activation and cytotoxic killing [18]. dMMR/MSI-H and pMMR/MSI-L Can be identified by immunohistochemistry and multiplex PCR. In various types of tumors, MSI-H has become a marker of immunotherapy responsiveness [19-21].

4 dMMR/MSI-H IMMUNOTHERAPY FOR CRC

Approximately 10% of CRCs are of the dMMR/MSI-H subtype, which is characterized by elevated neoantigen expression and high intraepithelial T cell infiltration. These characteristics make dMMR/MSI-H tumors particularly sensitive to ICIs, which can inhibit the negative regulation of cytotoxic T cells and promote T cell-mediated anti-tumor activity [22]. Previous clinical studies have shown the efficacy of ICIs in the late-line treatment of patients with advanced CRC [2, 4]. The results of the 2020 KEYNOTE-177 study [7] were announced for the first time, comparing pembrolizumab and classic chemotherapy combined with targeted therapy (FOLFOX or FOLFIRI ± cetuximab or bevacizumab) for dMMR/MSI-H metastasis The results show that pembrolizumab can significantly improve the dMMR/ MSI-H mCRC Patients' progression -free survival survival, PFS) (median PFS period: 16.5 months vs 8.2 months), the incidence of adverse events of grade 3 or above in the pembrolizumab treatment group was significantly lower than that in the control group. In 2021, ASCO reported an update on the results of the KEYNOTE-177 study [9], including health-related quality of life data, PFS analysis (24-month PFS rate: 48.3% vs 18.6%) and 12-month OS results after 2 interim analyses. Studies have shown that compared with standard chemotherapy combined with targeted therapy, the hazard ratio (HR) of OS is more favorable to pembrolizumab and has a tendency to reduce the risk of death. This study directly rewrote major guidelines, including ICIs As the first-line preferred option for the treatment of advanced CRC, pembrolizumab monotherapy has brought significant improvement in PFS and better safety in the first-line treatment of dMMR/MSI-H mCRC. The 2021 Chinese Society of Clinical Oncology guidelines point out that based on the results of the KEYNOTE 177 study, for unresectable dMMR/MSI-H For CRC patients, PD-1 inhibitor immunotherapy can be considered during conversion therapy or palliative care, and pembrolizumab is recommended as a Class I recommendation in the first-line palliative care regimen for dMMR/MSI-H patients. Recently, a research team found that the degree of MSI can predict the response of dMMR/MSI-H CRC to PD-1 blockade immunotherapy, inferring that future research may achieve dMMR/MSI-H tumor patients based on the intensity of microsatellite instability. Anti-PD-1 treatment provides more refined choices [23]. Clinical research on the application of ICIs in non-metastatic CRC is also underway. The single-arm NICHE study from the Netherlands [24] explored the use of ipilimumab combined with nivolumab for preoperative neoadjuvant immunotherapy for early-stage colon cancer. The results It is suggested that the pathological response rate and significant pathological response rate of dMMR patients reach 100% respectively. And 95%. For pMMR tumors, the pathological response rate also reaches 27%, and the protocol is safe and does not affect subsequent surgical treatment. The results of another VOLTAGE study [25] using nivolumab after neoadjuvant chemoradiotherapy showed that MSI-H Up to 60% of CRC patients achieved pathologic complete response (pathologic complete response) complete response (pCR) rate, and the pCR rate for MSS CRC patients has also reached 30%. These small sample clinical studies show the great potential of ICIs in the adjuvant and neoadjuvant treatment of CRC.

5 IMMUNOTHERAPY OF pMMR/MSI-L COLORECTAL CANCER

Unlike dMMR/MSI-H CRC patients, most pMMR/MSI-L CRC patients do not respond to ICIs; compared with dMMR/MSI -H, tumors with the pMMR/MSS phenotype generally exhibit lower tumor mutation burden and fewer tumor-infiltrating lymphocytes, leading to immune resistance in the tumor microenvironment. Accept and escape. In view of the fact that ICIs alone have no activity in advanced refractory CRC, Chen et al. [26] published a phase II clinical study in JAMA Oncology in May 2020, aiming to explore the combined use of PD-L1 and CTLA-4. Whether suppressive treatment of metastatic refractory CRC can improve patient survival, results show that the combined use of Durvalumab and Cyramza to suppress

immune checkpoints may be associated with prolonged OS in patients with advanced refractory CRC. In October 2020, Wang et al. [27] found that in pMMR/MSI-L CRC, inhibiting the modification of N-methyladenosine mRNA by depleting the methyltransferases METTL3 and Mettl14 enhanced anti-PD-1 treatment. Reaction. Tumors deficient in METTL3 or METL14 genes in vivo increase infiltrating CD8+T cells in the tumor microenvironment cells, promoting the secretion of interferon-γ (IFN-γ), CxCl9 and CxCl10. Mechanistically, METTL3 or METL14 deletion stabilizes STAT1 and IRF1 mRNA through Ythdf2, thereby promoting IFN-γ-STAT1- IRF1 signaling. In January 2021, Segal et al [28] evaluated the effect of the anti-PD-L1 agent Durvalumab and the CTLA-4 inhibitor Tremelimumab combined with radiotherapy in patients with chemotherapy-refractory pMMR mCRC. The results showed that this regimen has clinical effects and is safe. control. In February 2021, Monjazeb et al [29] demonstrated the addition of low-dose fractionated radiation in addition to the use of PD-L1/CTLA-4 blockers in a multi-center phase II study of patients with pMMR phenotype CRC. The feasibility and safety of low-dose fractionated radiation (LDFRT) or high-dose fractionated radiotherapy (HFRT) provide new ideas and theoretical guidance for the treatment of pMMR/MSI-L CRC. In general, for CRC patients with pMMR/MSI-L phenotype, ICIs have not yet demonstrated a breakthrough efficacy. Current research is mainly carried out in two aspects: looking for markers that can clearly predict the efficacy of treatment. For example, relevant studies suggest that in Among other types of solid tumors, patients with high TMB are better treated with ICIs [30]. However, there is currently a lack of research data on colorectal tumors, and ICIs combined with chemotherapy and targeted therapy are sought to improve the therapeutic effect. Therefore, ICIs are currently not used as a routine treatment option for patients with pMMR/MSI-L phenotype CRC and are only considered for clinical research.

6 ADVERSE REACTIONS OF ICIs

The use of ICIs will produce a series of adverse reactions related to the mechanism of action, which are completely different from other systemic therapies (such as cytotoxic chemotherapy) [31]. ICIs adverse reactions can affect multiple organs of the body, commonly seen in the skin, gastrointestinal tract, lungs, thyroid, adrenal gland, pituitary gland, musculoskeletal, kidney, nervous system, blood system, cardiovascular system and eyes, etc. Any changes in the body should be highly considered related to treatment [32]. In addition, 4%~ Immunotherapy may cause cancer cells to proliferate or accelerate in 29% of patients, a phenomenon known as hyperprogression, and some patients may experience pseudoprogression. The distinction between true progression, hyperprogression, side effects of immunotherapy drugs, and pseudoprogression is critical. A study published by Lee et al. [33] in JAMA Oncology in 2018 found that detecting ctDNA can reliably distinguish pseudo-progression from true progression in patients with metastatic melanoma treated with ICIs.

7 CONCLUSION

The therapeutic mechanism of ICIs for tumors is completely different from traditional chemotherapy and targeted therapy. The results of the KEYNOTE-177 study give new hope to patients with advanced CRC. For patients with dMMR/MSI-H CRC, ICIs have become the recommended first-line treatment option due to their good safety and effectiveness. For pMMR/ For patients with MSI-L CRC, ICIs have been used in the field of adjuvant and neoadjuvant treatment, and have also shown surprising efficacy. In the future, clinical research will focus on the application of ICIs to CRC patients at different stages of the disease to continuously expand treatment indications. But to our surprise, we saw that ICIs are not effective in pMMR/MSI-L CRC patients, and these patients account for more than 80% of all CRC patients. This means that most CRC patients are not suitable for ICIs. Therefore, Further studying its drug resistance mechanism, finding suitable biomarkers, and improving the efficacy of ICIs combined with chemotherapy and targeted therapy are urgent problems that need to be solved and are also the focus of clinical research.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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