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REVIEW

Immune Checkpoint Inhibitor-Based Combination Therapy for Colorectal Cancer: An Overview

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Abstract: Colorectal cancer (CRC) is one of the most common diseases in the world. Tumor immunotherapy is an innovative cancer treatment that acts by activating the human body's autoimmune system. Immune checkpoint block has been shown to be effective in DNA deficient mismatch repair/microsatellite instability-high CRC. However, the therapeutic effect for proficient mismatch repair/microsatellite stability patients still requires further study and optimization. At present, the main CRC strategy is to combine other therapeutic methods, such as chemotherapy, targeted therapy, and radiotherapy. Here, we review the current status and the latest progress of immune checkpoint inhibitors in the treatment of CRC. At the same time, we consider therapeutic opportunities for transforming cold to hot, as well as perspectives on possible future therapies, which may be in great demand for drug-resistant patients.

Keywords: immune checkpoint inhibitors, colorectal cancer, PD-1/PD-L1, combination therapy, DNA mismatch repair

Introduction

The incidence and mortality rates of colorectal cancer (CRC) are the third highest in the United States, representing a great threat to the health of the population.[1] At present, CRC is treated with surgery, chemotherapy, radiotherapy, immunotherapy, and targeted therapy. However, because the initial symptoms are not obvious, patients often have poor prognosis in the late stages, so that the 5-year overall patient survival rate is less than 15%.[2] Reducing the metastasis and recurrence in late-stage patients is of great significance. Immune checkpoints refer to a series of molecules that are expressed in the immune cells. They can regulate the degree of immune activation and play an important role in preventing the occurrence of autoimmune effects.[3] The combination of programmed death receptor and its ligand results in T cell failure and inability to kill tumor cells. Moreover, the tumor cells can escape the immune surveillance of the host.[4,5] Therefore, effectively blocking the activation of immune checkpoints can improve the aggressiveness of the host immune system to tumor cells.

Immune cells are common normal cell types that live in association with cancer cells. If there are more immune cells around the cancer, the tumor is categorized as hot. The opposite is true for cold tumors. Immunotherapy techniques for CRC have been developing rapidly. Clinical trials have included advanced, first-line, second-line, and various other types of adjuvant therapy.[6,7] Continuous progress in precise tumor treatments, second-generation gene sequencing, and other technologies have obviated the original tumor division based on tumor location and organ, instead introducing the population screening method based on different new biomarkers. Recommendations for the treatment of the same cancer species of different molecular types are also different.[8–10] The mismatch repair (MMR)/microsatellite instability (MSI) system is the most important indicator for CRC classification, which is used to formulate treatment strategies. MSI is a code-shifting mutation of microsatellites in tumor cells caused by the insertion or deletion of duplicate units.[11] The DNA MMR system fights against these errors by identifying and repairing DNA damage and correcting base insertion, deletion, or mismatch caused by the wrong cycle in the DNA replication process. The defect of mismatch repair function (dMMR) is characterized by the lack of the MMR protein.[12,13] When the MMR system is dysfunctional or mutated, these genetic errors will not be corrected, so that they will be permanently integrated into the tumor DNA, which is highly

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unstable (MSI-H). The MMR protein is normally expressed in mismatch repair proficient (pMMR), which is categorized by low instability (MSI-L) and stability (MSS).[14,15] According to the above classification, CRC will enter a new era of differential treatment for the same disease.

Classic Immune Checkpoint Inhibitors (ICIs) for dMMR/MSI-H

T cells can fight against tumor immune responses by increasing cytotoxic responses after they receive an effective and lasting stimulus signal. This stimulus signal includes co-stimulatory signals to enhance immunity and co-inhibitory signals to suppress immunity, which are immune checkpoints.[16] Tumors inhibit the immune system to promote tumor immune escape and tolerance through overexpression of immune checkpoints, thus promoting tumor cell growth.[17,18] ICIs can effectively block the binding of inhibitory checkpoints and ligands, reactivate T cells, and monitor the invasion of immune tumor cells in the body.[19] They include programmed cell death receptor 1 (PD-1), programmed cell death receptor ligand 1 (PD-L1), cytotoxic T lymphocyte associated antigen 4 (CTLA-4), and others.[20,21] Studies have confirmed that ICIs have a significant effect in patients with dMMR/MSI-H who can benefit from them.

PD-1/PD-L1

PD-1, also known as CD279 (differentiation cluster 279), is an important immunosuppressive molecule. In 1992, Ishida et al first found and named PD-1 in gene screening involved in cell apoptosis.[22] PD-1/PD-L1 can regulate the immune system and promote self-tolerance by downward regulating the immune system response to human cells, as well as by inhibiting the inflammatory activities of T cells.[23] This can prevent autoimmune diseases. Tumor cells may induce tolerance and apoptosis of T cells through PD-1/PD-L1 and achieve immune escape by inhibiting the proliferation and activity of T cells and promoting epithelial mesenchymal transformation.[24]

In 2015, Le et al first found that dMMR/MSI-H patients benefit from ICIs, bringing them new hope.[25] The representative ICIs drugs are pembrolizumab and nivolumab, which have been approved for the third-line or even second-line treatment of PD-L1-positive metastatic CRC (mCRC). The key Phase II study KEYNOTE-016 was the first to reveal the relationship between the MMR status and ICI efficacy. In this study, the objective response rate (ORR) in mCRC patients initially included in the dMMR and pMMR groups after receiving the pembrolizumab treatment was 40% and 0%, respectively. Later, the dMMR/MSI-H patients were further treated, resulting in an ORR of 52%. The 2-year progression-free survival (PFS) and overall survival (OS) rates were 59% and 72%, respectively.[26] The KEYNOTE-028 study verified that among 20 different types of tumors, only the patients with MSI-H advanced CRC went into partial remission.[27,28] The KEYNOTE-164 study further introduced PD-1 inhibitor into clinical application. Its research results suggested that the ORR of patients who had received lines 2 and 1 treatments before administering pembrolizumab were 32.8% and 34.9% respectively. Restarting the treatment after progress has been achieved, making some patients relieved or stable.[29] Furthermore, the KEYNOTE-177 study compared the dual drug chemotherapy of pembrolizumab combined with vascular endothelial growth factor (VEGF) or epidermal growth factor receptor (EGFR) monoclonal antibody. The results showed that the median PFS of a single drug was 16.5 months and the ORR was 45.1%, while the values for the chemotherapy group were 8.2 months and 33.1%, respectively. The above experiments confirmed that pembrolizumab could be used as the first-line standard treatment for patients with dMMR/MSI-H. The National Comprehensive Cancer Network (NCCN) diagnosis and treatment guidelines have also been successfully rewritten based on this information.[30,31] Another key phase II study CheckMate-142 single drug treatment cohort showed that the single drug treatment of nivolumab resulted in an ORR in the dMMR/MSI-H patients of 31.1%, with the median PFS of 14.3 months and the OS rate of 73% at 12 months.[32] Current research studies have mainly focused on the combined application of PD-1 inhibitors with other immunosuppressants, which will significantly improve the therapeutic effect without increasing adverse reactions.

Atezolizumab is an important representative of PD-L1. The COMMIT trial is a Phase III open label in-progress study that compares the efficacy and safety of atezolizumab versus mFOLFOX6/bevacizumab, where PFS serves as the primary endpoint (NCT02997228). The latest research has demonstrated that many new PD-1 and PD-L1 inhibitors,

such as doxalimab, cindilizumab, tirelizumab, and duvalizumab, showed effective anti-tumor activity in patients with advanced solid tumors.[33–35]

CTLA-4

CTLA-4, also known as CD152 (differentiation cluster 152), is a protein receptor that acts as an immune checkpoint that downregulates the immune response. Golstein et al identified CTLA-4 in 1987.[36] In 1995, Tak Wah Mak and Arlene H. Sharpe independently published the discovery about the function of CTLA-4 as a negative regulator of T cell activation by knocking out mouse genes.[37] CTLA4 is constitutively expressed in regulatory T cells, but is only up-regulated in conventional T cells after activation, which is particularly significant in cancer.[38] Recombinant CTLA-4 Ig can effectively and specifically inhibit cellular and humoral immune responses in vivo and in vitro and has significant therapeutic effects on transplant rejection and various autoimmune diseases with very low toxicity and side effects.[39,40] It is currently considered to be a promising new immunosuppressive drug, especially ipilimumab and tremelimumab.

Ipilimumab is an important inhibitor acting on CTLA-4. After their combination, the interaction between CTLA-4 and its ligand CD80/CD86 is blocked and the activation and proliferation of T cells enhance the tumor immune response.[41,42] However, the results of ipilimumab's single use are not satisfactory. At present, it is believed that nivolumab plus ipilimumab has a very positive clinical effect in dMMR/MSI-H patients, such that 54.6% of them can objectively experience relief.[32] Although the research on CTLA-4 has begun early on, there is a still a lack of drugs on the market, which indicates that the research progress is relatively slow. At present, many drugs are still in the exploration and adjustment Phases I and II and are generally used together with other PD-1 drugs to achieve better therapeutic effects. It is possible that other targets can replace CTLA-4 to develop more effective drugs.[43–45]

Other Immune Checkpoint Molecules

With the in-depth study of immune regulation and tumor microenvironment, more targets have been discovered and added to the existing clinical research investigations, such as T cell immune receptor with Ig and immunoreceptor tyrosine-based inhibitory motif domains (TIGIT), lymphocyte activation gene-3 (LAG-3), natural killer group 2 member A (NKG2A), and T cell immunoglobulin domain and mucin domain-3 (TIM-3). There are many current related clinical studies on this subject.[23,46–48] A Phase I clinical trial on pembrolizumab combined with anti-LAG-3 antibody favezelimab in 89 previously treated MSS mCRC patients showed four patients with partial remission and one patient achieving complete remission. The median remission duration was 10.6 months and the toxicity was controllable, suggesting that combined immunotherapy may have survival benefits in patients with MSS type cancer.[49]

TIM-3 and TIGHT are also emerging immune checkpoint molecules, which might bring new hope to cancer patients who cannot benefit from PD-1 antibody use. Several drugs targeting TIM-3 and TIGHT, such as BMS-986258, relatimab, and tiragolumab, have entered clinical trials[50–52] Recently, Tiganis et al suggested that there is a new immune checkpoint on the endoplasmic reticulum of tumor-infiltrating T cells known as protein tyrosine phosphatase 1b (PTP1B). The high expression level of PTP1B inhibits the proliferation, while its knockout promotes the activation of the STAT5 signaling pathway in T cells, thereby inhibiting tumor growth. It can also be combined with PD-1 inhibitor and chimeric antigen receptor T-cell immunotherapy (CAR-T) cells to achieve better anti-tumor effects.[53] Recombinant tumor necrosis factor receptor superfamily member 9 agonist combined with PD-L1 can effectively activate and expand tumor-specific cytotoxic T cells and enhance tumor control and killing. Related drugs, such as RG-7827, urelumab, and utomilumab, are under development.[54,55] These new targets are expected to greatly improve the progress of tumor immunotherapy. However, there has been no breakthrough in the effect of single-use drugs at the immune checkpoint. More and more studies have focused on the combination of immunotherapy schemes, and it has been confirmed that they do not cause a significant increase in adverse reactions.[56,57]

Combined Immunotherapy

In 2018, Overman et al reported the effect of dual immunotherapy of nivolumab plus ipilimumab in the second- and posterior-line treatments of dMMR/MSI-H mCRC in the CheckMate142 study.[32] A total of 119 patients were included in

the study, which had an ORR of 55%, and the OS rates after 9 and 12 months of 87% and 85%, respectively. The above results showed that nivolumab combined with ipilimumab had a higher ORR than nivolumab alone, suggesting that PD-1/PD-L1 inhibitors combined with other immune checkpoint blockers improve the treatment effect.[32,58,59] Anti-CTLA4 therapy has resulted in an enhanced antigen-specific T cell-dependent immune response, while anti PD-1 seemed to reactivate the ability of CD8+T cells to cleave cancer cells. This experiment moves immunotherapy from the third-line selection to the first-line treatment. At present, pembrolizumab and nivolumab alone or in combination with CTLA-4 blockers (such as ipilimumab) have been approved by the US FDA for clinical use in the treatment of mCRC with dMMR/MSI-H. Additional experiments are still in progress. For example, CheckMate 8HW is exploring the efficacy of three regimens, including nivolumab alone, nivolumab combined with ipilimumab, and chemotherapy selected by the researchers (NCT04008030).[60] The latest studies have found that blocking the expression of CD73 in immune circulation can improve the effect of combined immunity, and the molecular mechanism related to improving the effect of dual immunotherapy needs to be further explored.[31]

Adjuvant and Neoadjuvant Therapy

It is well known that MSI-H CRC has a poor postoperative chemotherapy response, and immunotherapy can be used to improve it. At present, there are three major clinical trials. The ATOMIC study (NCT02912559) has explored the effect of atezolizumab combined with single chemotherapy with DFS as the end point.[61] The POLEM trial (NCT03827044) is a multicenter, three-stage, randomized clinical study on adjuvant treatment of dMMR colon cancer with avelumab and fluoropyrimidine.[62] These studies are still in progress and their results are expected.

A new adjuvant therapy strategy is to generate a better immune response before tumor resection. NICHE is the first phase II clinical trial on early neoadjuvant therapy. The study patients underwent colon cancer surgery no later than 6 weeks after receiving the first immunotherapy treatment. The remission rate of dMMR colon cancer patients receiving neoadjuvant immunotherapy reached 100%, and only 10% of patients had related toxic reactions. However, the remission rate in pMMR was only 27%.[63] The VOLTAGE study also showed that 60% of patients with MSI-H achieved pathological complete remission (pCR) after preoperative radiotherapy and chemotherapy combined with nivolumab, where only three patients experienced immune related adverse events (AEs) and all had recovered.[64] The new adjuvant treatment monotherapy regimen of nivolumab plus ipilimumab or pembrolizumab has been added to the 2021 NCCN CRC guidelines.[30] A small Phase 2 clinical trial has recently reported that 12 rectal cancer patients received dostarlimab treatment with a clinical complete remission rate of 100%. No disease recurrence was observed during the follow-up period, and none of the patients reported adverse reactions of grade 3 or above, which is a significant step in the fight against cancer.[65] In addition, the combined new auxiliary scheme of star combination nivolumab and ipilimumab also produced a 100% response rate in patients with dMMR colon cancer.[66]

Although the dMMR/MSI-H population significantly benefited from the treatment with immunosuppressive agents at immune checkpoints, the total number of beneficiaries was about 5%. Treating patients with pMMR/MSS mCRC with ICIs alone is not ideal[67] and relevant methods need to be further explored. On one hand, the dominant population has been screened based on the MMR classification. Moretto et al reported that homologous recombination defect tumors in CRC patients with pMMR/MSS were a significantly different subgroup with unique molecular and prognostic characteristics, which could be used to investigate the potential efficacy of drugs worth exploring.[68] On the other hand, it is necessary to improve the ICI dosage selection and actively seek other drug combinations to improve the therapeutic effect.[69,70]

Combination Therapy for pMMR/MSS

The pMMR/MSS population has no obvious benefits due to its inherent immunosuppressive characteristics, low tumor lymphocyte infiltration level, and low tumor mutation burden (TMB). How to explore such populations, overcome their limitations, and transform cold tumors into hot is very important.[71] The combination of ICIs and other treatment schemes for pMMR/MSS CRC patients may achieve a certain effect due to the change in tumor microenvironment, while the combination of ICIs and other treatment schemes for dMMR/MSI-H CRC patients may improve the effect of immunotherapy due to the improvement in TMB.[72] From the aspects of tumorigenesis, angiogenesis, metastasis, tumor immunity, and other key carcinogenic pathways, using various joint means to regulate the immune microenvironment

of such tumors so that drugs can have a synergistic anti-tumor effect with ICIs will eventually transform the inherently cold tumors into hot, which can be effectively recognized and targeted by the activated immune system.[73,74]

Combined Targeted Medicine

VEGF/VEGFR

Recognized basic research has confirmed that VEGF and VEGFR are important molecules that control tumor angiogenesis. Their inhibitors can reduce tumor angiogenesis, increase the degree of T cell response, and have a synergistic effect when combined with immunotherapy.[75] Multi-target tyrosine kinase inhibitors (TKIs), which mainly inhibit VEGF or VEGFR, have become the most promising combination drugs.[76]

Regorafenib is a multi-kinase inhibitor that targets several receptor tyrosine kinases involved in angiogenesis and metastasis (VEGFR1, VEGFR2, VEGFR3, FGFR1, FGFR2, TIE2, and PDGFRs), tumorigenesis (KIT, RET, and RAF1), and tumor immunity (CSF1R). The Japanese REGONIVO study reported that the exploratory phase I b study using nivolumab combined with low-dose regorafenib for the treatment of refractory MSS type CRC and gastric cancer showed that the ORR in mCRC was as high as 33.3%, 1-year PFS rate was 41.8%, and 1-year OS rate was 68.0%.[77] In the second phase of the French REGOMUNE and North American studies (NCT04126733), the results showed that PD-1 inhibitors combined with regorafenib did not achieve good results, with an ORR level of <10%.[78–80] The REGNIVO5 and REGOTORI6 studies in North America have shown inconsistent results,[81,82] largely due to the extensive study heterogeneity in terms of design, geographical region, patient characteristics, and sample size.[83] Lenvatinib is also a TKI type, which can inhibit the kinase activity of VEGF receptor and pathological angiogenesis of other tumors. LEAP-005 study is a phase II multi cohort clinical trial on lenvatinib combined with pembrolizumab in previously treated patients with solid tumors. Its ORR and median OS were reported to be 22% and 10.6 months, respectively.[84] At present, there are three phases in the LEAP-017 study (NCT04776148) and their results for using pembrolizumab in combination with lenvatinib in CRC patients are promising.

Bevacizumab is a monoclonal antibody that can inhibit VEGF production. The BACCI study in 2019 has reported that the combination of atezolizumab with bevacizumab and other chemotherapy drugs effectively improved ORR, but the median PFS and OS were not significantly improved.[85] The AtezoTRIBE study at the ESMO meeting in 2021 showed that significant differences between groups were generated after the treatment with atezolizumab plus bevacizumab combined with FOLFOXIRI or fluorouracil. However, clinician approval still needs further discussion.[86] At present, some RCT studies are still exploring whether the combination of standard first-line chemotherapy and bevacizumab-based immunotherapy is effective.[87–89]

Fruquintinib is a new, oral, highly selective targeting drug for VEGFR. It can inhibit the formation of tumor neovascularization by inhibiting VEGFR phosphorylation and downstream signals on the surface of vascular endothelial cells and play a role in inhibiting tumor growth and metastasis. The results of a phase I b study suggested that the ORR in patients with mCRC who failed to receive second-line treatment with fruquintinib and cindilimab was 22.7%, while the median PFS was 5.6 months.[90] Another study confirmed that the ORR and median PFS after the mCRC treatment with fruquintinib combined with a new PD-1 inhibitor geptanolimab reached 26.7% and 7.33, respectively, and 25% and 5.45 months, respectively, in MSS patients.[91] Although its current sample size is small, this study has great potential.

The specific mechanism for the difference in efficacy between anti-angiogenic targeted drugs with different mechanisms and immunotherapy is unknown. It is speculated that the reason may be that TKI drugs are multi-target. In addition to inhibiting the VEGF/VEGFR pathway, TKI drugs may also inhibit targets related to immune regulation, such as platelet-derived growth factor receptor (PDGFR), angiopoietin-2 receptor (TIE2), and colony-stimulating factor 1 receptor, and have stronger synergy with immunotherapy.[92–94]

EGFR

EGFR is a member of the epidermal growth factor receptor (HER) family, which includes HER1 (erbB1, EGFR), HER2 (erbB2, NEU), HER3 (erbB3), and HER4 (erbB4).[95,96] Studies have shown that EGFR is overexpressed or abnormally expressed in many solid tumors.[97,98] It is also related to the inhibition of tumor cell proliferation, angiogenesis, tumor invasion, metastasis, and apoptosis.[99]

Panitumumab is a monoclonal antibody targeting EGFR. The LCCC1632 study (NCT03442569) evaluated the efficacy and safety of panitumumab and nivolumab plus ipilimumab in the treatment of patients with KRAS, NRAS, BRAF wild-type, and MSS metastatic CRC. The ORR was 35%, and the median PFS was 5.7 months.[100] The AVETUX (NCT03174405) study explored the effects of cetuximab, avelumab, and conventional chemotherapy. The median PFS was 11.1 months, but the rate of adverse reactions was high, mainly including dryness, acne-like dermatitis, rash, hypomagnesemia, and vomiting.[101,102] Therefore, more clinical trials will be needed to optimize the dosage and joint use plan and determine the minimum toxicity plan, which will bring health benefits to patients and not damage their quality of life.

MAPK/MEK

Mitogen-activated protein kinase (MAPK) pathway has three levels of signal transmission: MAPK, MAPK kinase, and kinase of MAPK kinase. These three kinases can be activated in turn and jointly regulate many important physiological/pathological effects, such as cell growth, differentiation, stress, and inflammatory reaction. MEK is a key factor in this pathway, and its abnormal function leads to serious tumor diseases.[103] Many studies have confirmed that MEK inhibitors can enhance tumor immunity, while helper T cells can maximize the synergistic effect on immunotherapy. However, further exploration of the CRC treatment is needed.[104,105] The IMblaze370 test showed that the combination of atezolizumab and cobimetinib had an effective rate of 8%. Compared to the single-drug group of atezolizumab and regorafenib, the OS for the combination of atezolizumab and cobimetinib was not significantly different, and the incidence of grade 3–4 AEs increased significantly to 64%.[106]

BRAF/RAS

Kirsten rat sarcoma viral oncogene (KRAS) is the most common mutation member of the RAS family and the most common oncogene driver in human cancer. About 30–40% of patients with CRC have a KRAS mutation.[107] Previous CheckMate 142 and KEYNOTE-164 studies have both investigated the KRAS/RAS mutation. CheckMate 142 results suggested that the ORR in mutant patients using nivolumab was lower than that in wild-type patients, while KEYNOTE-164 results showed that the ORR in different patients using pembrolizumab was similar.[29,32,59] Therefore, it is of great significance to further determine the joint role of KRAS and PD-1.

In 2018, a Phase 1b/2 study evaluated the safety and effect of binimetinib combined with nivolumab or nivolumab plus ipilimumab. The results showed that although the adverse reaction rate for KRAS inhibitor combined with a single drug was 44.44%, while that of two combined drugs was 40.75% with a median ORR of 7.4 months, the treatment showed preliminary efficacy, although its safety needs to be further optimized and improved.[108] A trial report on BRAF V600E mutation mCRC patients in 2020 has shown that the ORR for PD-1 monoclonal antibody combined with BRAF inhibitor (dabrafenib)+MEK inhibitor (trametinib) was 35%, while the ORR for MSS patients who had not received targeted therapy before was 45%. In 2022, a new KRAS inhibitor adagrasib (MRTX849) showed that MRTX849 alone achieved an ORR of 87%, while cetuximab combined with targeted drug achieved a stronger anti-cancer effect. Furthermore, 100% of patients were in stable condition and their tumors shrank to varying degrees.[109] The pMMR patients with BRAF/RAS mutations can significantly benefit from combined immune targeted therapy and even use double target therapy to improve the effect.[110]

Other Targets

Based on statistical analysis, human epidermal growth factor receptor-2 (HER2) amplification or overexpression is found in 3–5% of patients with advanced or metastatic CRC.[111] In 2022, the FDA granted priority approval to the new combination therapy of tucatinib and trastuzumab. In the treatment of adult patients with HER2-positive CRC, the confirmed ORR was 38.1% in 84 patients receiving tucatinib and trastuzumab, although other new drugs were also under study.[112] In addition, about 1–5% of colon cancer patients have neurotrophin receptor kinase fusion, especially with MSI-H. The results of the first targeted drug larotrectinib, which is not limited to cancer species, showed that the ORR in CRC patients was as high as 47%, which means that nearly half of all CRC patients' lesions were significantly reduced or even disappeared. In addition, 42% of patients were in stable condition, and the disease control rate reached 89%.[113] There

will be more effective and targeted drugs with the improvement of gene detection technology in the future, which will be used in clinical standardization and help tumor diagnosis and treatment.

Combined Conventional Chemotherapy

Theoretically, there is a synergistic effect between chemotherapy and immunotherapy. Tumor cells are exposed to antigens after being attacked by chemotherapy drugs to induce an immune response, which can also reduce the inhibition of tumor cells in immunity.[68,101] Therefore, whether immunotherapy plays an effective role in pMMR patients with the assistance of chemotherapy drugs has piqued scientists' interest, but the results have been disappointing.

In the KEYNOTE-651 study (NCT03374254), pembrolizumab combined with mFOLFOX7 (cohort B) or FOLFIRI (cohort D) has been used as the first- or second-line treatment for advanced CRC, respectively. The results showed that one case in cohort B progressed, the PFS in cohort D was 17.4 months, and the ORR was 16%.[114] The BACCI study (NCT02873195) included patients with standard treatment failure, and capecitabine plus bevacizumab and atezolizumab were used as the posterior-line treatment. The OS and PFS in the two groups were not significantly improved, but the ORR increased from 4.35% to 8.54%.[85] The METIMMOX study adopted the FLOX protocol plus nivolumab group to compare to the FLOX protocol alone. The results showed that the median PFS in the combined group was 6.6 months and 5.6 months in the single FLOX group. These results were not encouraging.[115] The AtezoTRIBE and MODUL studies were conducted to investigate the first-line treatment for unresectable advanced CRC. Atezolizumab plus bevacizumab combined with FOLFOXIRI or fluorouracil was used for treatment, indicating that its combination with FOLFOXIRI prolonged the PFS of patients with metastatic CRC. However, PFS and OS were not significantly improved by fluorouracil use.[86,116]

Combined Radiotherapy

Radiotherapy induces immunogenic cell death using radiation to enable T cell response with anti-tumor activity. This method can promote the release of tumor-related antigens. Many antigen-presenting cells enhance the presentation of tumor antigens, recruit more immune cells, change the tumor microenvironment, and improve the anti-tumor effect.[117,118]

A previous phase II trial suggested that the distant tumors in MSS mCRC patients treated with a combination of ipilimumab and nivolumab and radiotherapy were reduced in size, while an ORR of 12.5% was observed in patients. This study showed its potential feasibility.[119] The VOLTAGE study showed that 30% of MSS patients achieved pCR after preoperative radiotherapy and chemotherapy followed by five cycles of nivolumab and surgical resection. Moreover, 60% of patients with MSI-H reached pCR.[64] A multicenter phase II study AVANA (NCT03854799) found that 23% of patients reached pCR with preoperative radiotherapy and chemotherapy combined with avelumab, and 61.5% of them had major pathological reactions.[120] The PANDORA study recruited 60 patients who had a clinical response percentage of 81.8%, while 23 patients (41.8%) experienced AEs related to the durvalumab treatment. This study showed a promising activity of neoadjuvant chemo-radiotherapy plus durvalumab in terms of pCR rate and safe toxicity profile.[121] Other trials included AveRec (NCT03299660), INNATE (NCT04130854), and TARZAN (NCT04017455).[122] This shows that immune combined chemotherapy can have a certain effect. The choice of radiotherapy mode (dose, segmentation mode, and treatment sequence) remains under investigation and more research is expected.

Combined Oncolytic Virus

Oncolytic viruses are natural or recombinant viruses that can selectively infect and kill cancer cells, but do not harm normal cells. Their principle is to selectively infect tumor cells via genetic modification of viruses with weak pathogenicity using the inactivation or defect of tumor suppressor gene in target cells to replicate in large numbers and destroy tumor cells.[123] At the same time, they can also stimulate the immune response and attract more immune cells to continue to kill residual cancer cells.[124,125] The combination of T-VEC and pembrolizumab, an oncolytic virus drug, in the treatment of melanoma showed an ORR of up to 62%, of which 33% of patients were in complete remission.[126] A phase I/II study on the treatment of MSS mCRC with Pexa Vec combined with durvalumab, a tumor lytic virus drug, preliminarily demonstrated that it is well tolerated in the treatment of pMMR patients and showed a possible activity.[127] In addition, a phase I b trial on the oncolytic virus drug talimogene laherparepvec combined with atezolizumab in the treatment of CRC patients with liver metastasis is presenting being investigated.

Combined Tumor Vaccine

Tumor vaccine development has become a research focus in recent years. Its principle is to introduce tumor antigens into patients in various forms, overcome the immunosuppressive state caused by tumors, enhance immunogenicity, activate patients' own immune system, and induce cellular and humoral immune responses to control or eliminate tumors. In 2010, the FDA approved the first tumor vaccine sipuleucel-T for the treatment of prostate cancer.[128] OncoVAX is under development in the field of CRC. A phase III randomized clinical study included 254 patients with phase II and III colon cancer. It demonstrated that the recurrence risk in the vaccine group patients was lower than that in the surgery group patients. Further research confirmed that OncoVAX had no significant effect on patients with stage III colon cancer. It can prolong the recurrence-free interval (RFI) in patients with stage II colon cancer, reduce the total recurrence risk, significantly prolong the recurrence-free survival period in the vaccine group patients, reduce the risk of recurrence or death, and improve the overall OS.[129] A subsequent phase III clinical study on colon cancer found that the OncoVAX RFI was significantly delayed, and the 5-year OS and relapse-free survival rates were improved.[130] PolyPEPI1018 is a ready-made polypeptide vaccine that contains 12 immunogenic epitopes derived from seven kinds of cancer-testis antigen (CTA) frequently expressed in CRC patients. The OBERTO study has evaluated the safety and effectiveness of PolyPEPI1018 vaccine in maintenance treatment. The results showed that all patients had no vaccine-related serious adverse reactions, and some patients experienced sustained clinical benefits.[131] Further experiments confirmed that PolyPEPI1018 can effectively restore the immune response to CTA. The use of PolyPEPI1018 vaccine and maintenance therapy is safe and has demonstrated the early clinical activity of MSS mCRC tumors.[132] Based on the above evidence, the application value of tumor vaccine in MSS type mCRC patients is worth studying.

Combined CAR-T Cell Therapy

CAR-T treatment involves collection and isolation of T cells from the patient's blood, followed by gene modification to enhance their targeting and killing ability against cancer cells. After many T cells are cultured and expanded in vitro, they are imported into the patient's body where they continue to reproduce, finally identifying cancer cells in vivo and destroying them.[133–135]

Carcinoembryonic antigen (CEA) is an important tumor marker in CRC. It is highly expressed in CRC cells and is a potential target for CRC treatment.[136,137] In a phase I clinical trial on CEA, three mCRC patients received the CAR-T treatment, and their serum CEA levels decreased significantly. One patient had lung metastasis and liver metastasis, and all patients had severe colitis.[138] Safety and effectiveness tests were also conducted in another experiment, where no obvious treatment-related toxic reactions were found.[139] Three CUAD-101 dose levels were evaluated in the AlloSHRINK I study. The results showed that nine cases obtained a median PFS of 3.9 months. The treatment was well tolerated, and no treatment-related AEs above grade 3 occurred.[140] Another study included 21 mCRC patients, where the ORR for dose level 1 ($1x10^6$ cells/kg) was 15.4% and 50% for dose level 2 ($2x10^6$ cells/kg). The most common AEs were cytokine release syndrome and diarrhea.[141] The Immunological checkpoints and combination therapies are shown in Figure 1.

Future Perspectives

There is growing evidence that CRC is associated with altered gut microbiota. Specifically, the microbiota shapes the host's immune system by modulating local and systemic immune responses, influencing the efficacy of cancer treatment. While many of the studies are still in their early stages, the results presented are strongly correlated. Therefore, in the future, scientists should combine various disciplines, such as microbiology and molecular biology, to establish a reasonable ecological model and promote the development of precision treatment to benefit patients.

More and more basic experiments and clinical studies suggest that immunosuppression has potential in the treatment of CRC.[142] At present, the MMR or MSI status is still considered to be the most important distinguishing indicator. Further exploration of immune markers is necessary for more targeted clinical application of drugs. In addition, immune drug resistance and immune escape are the main obstacles to achieving effective immunotherapy. Even though there have been many related studies addressing this issue, it is difficult to control all aspects of the immunosuppression process due to its dynamic continuity. Future basic research studies with a strong foundation are needed to develop more accurate

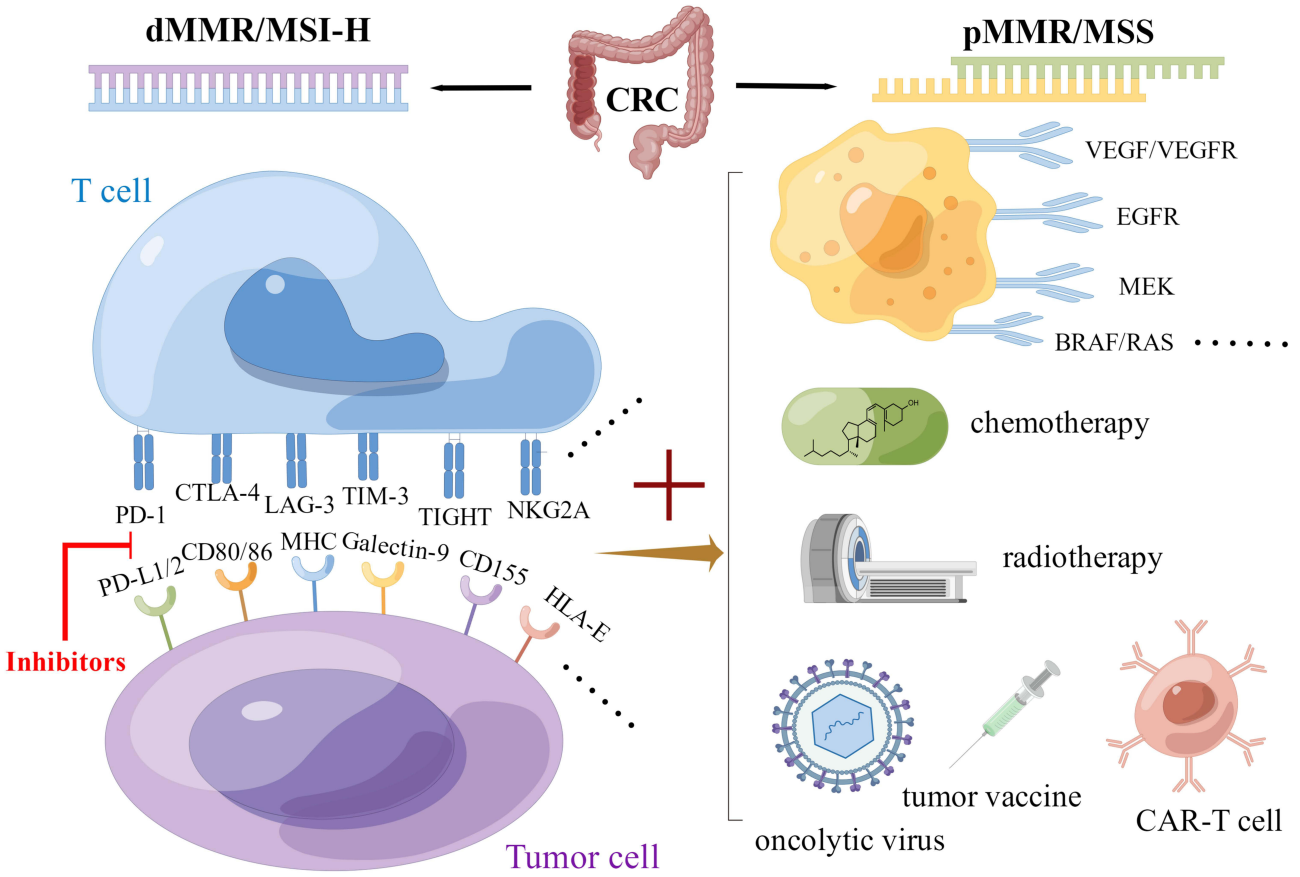

Figure 1 Immunological checkpoints and combination therapies of CRC. The mismatch repair (MMR)/microsatellite instability (MSI) system is the most important indicator for CRC classification. ICIs have a significant effect in patients with dMMR/MSI-H who can benefit from them.The pMMR/MSS population has no obvious benefits due to its inherent immunosuppressive characteristics, low tumor lymphocyte infiltration level, and low tumor mutation burden (TMB). The combination of ICIs and other treatment schemes for pMMR/MSS CRC patients may achieve a certain effect due to the change in tumor microenvironment (By Figdraw).

strategies.[143] From traditional radiotherapy and chemotherapy to targeted therapy and immunotherapy, basic research studies have resulted in continuous progress in the area of clinical tumor treatment. More targets have been identified and more drugs have been explored.[144,145] At the same time, combination therapy has also become more prominent. Strategies for adjusting the order and dosage of ICIs and combination drugs in various ways, achieving the best outcomes, and reducing the side effects while maintaining a safety profile still require a lot of research. It is expected that more optimized and accurate treatment techniques will be of benefit to CRC patients.

Disclosure

The authors report no conflicts of interest in this work.

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