

IcIs Treatment for Different MSI Colorectal Cancer: Theoretical Basis, Status Quo And Outlook

Wenjie Gu¹, Haotian Liu¹ and Kuo Ma^{2, *}

¹ Nanjing Tech University, Nanjing, China

² South China Normal University, Guangzhou, China

* Corresponding Author Email: 2023023087@m.scnu.edu.cn

Abstract. As the third cancer worldwide, the incidence and the cancer-related mortality is both high in colorectal cancer (CRC) patients. The treatment of CRC has standard methods, including radiotherapy, chemotherapy and other general therapy. However, these systemic therapies are not specific, which are also toxic for normal cells and show many side effects in patients. New immunotherapeutic strategies have changed the landscape of treatment of metastatic CRC (mCRC), especially immune checkpoint inhibitors (ICIs). After research, the condition of microsatellite instability (MSI) has proven to be one of the main influencing factors of ICIs' efficacy. This review comprehensively analyses the possible mechanisms underlying the varying efficacy of ICIs in the treatment of different MSI tumors and evaluates potential therapeutic strategies that offer possible ways to overcome resistance mechanisms.

Keywords: Colorectal cancer (CRC), immune checkpoint inhibitors (ICIs), microsatellite instability (MSI), drug resistance.

1. Introduction

Colorectal cancer (CRC) is the third cancer worldwide. With the development of tumor immunology, tumor immunotherapy has become an important means to treat CRC, especially immune checkpoint inhibitors (ICIs). ICIs have changed the prognosis of some patients with CRC and improved the survival, showing the optimistic therapeutic efficacy. Study have found that one of the important factors affecting ICIs for CRC therapeutic is microsatellite instability (MSI) [1]. According to the condition of MSI, CRC can be divided into high-microsatellite instability (MSI-H) and low-microsatellite instability (MSI-L). The current therapeutic effect of ICIs on MSI-H patients is satisfactory, but only a few MSI-L patients can benefit from ICIs. In addition, drug resistance may also occur during the treatment of ICIs [1]. For the above problems, the emergence of many immune combinations therapy has enabled most CRC patients to obtain significant treatment strategies, this article will review the theoretical basis, status quo, and outlook of ICIs in the therapeutic of different MSI types of CRC.

2. The theoretical basis of ICIs for treatment CRC

The T-cell infiltration to the tumor bed has always been related to good prognosis, which shows that immunoediting may play a role in controlling tumor growth [2]. Through major histocompatibility complex (MHC) binding to the T-cell receptors (TCR), T cells are activated by TCR stimulation and express programmed cell death protein 1 (PD-1), which can bind to its ligand (programmed cell death ligand 1, PD-L1) that are present in antigen-presenting cells (e.g., tumor cells), When PD-1 binds to its ligand, it can induce T-cell exhaustion. Thus, in CRC, tumor cells are able to suppress the anti-tumor response of T cells by up-regulating PD-L1. ICIs target PD-1 or PD-L1, blocking this inhibition and unleashing the anti-tumor activity of cytotoxic T lymphocytes (CTLs) through promoting the activation and proliferation of T cells (Fig. 1) [3].

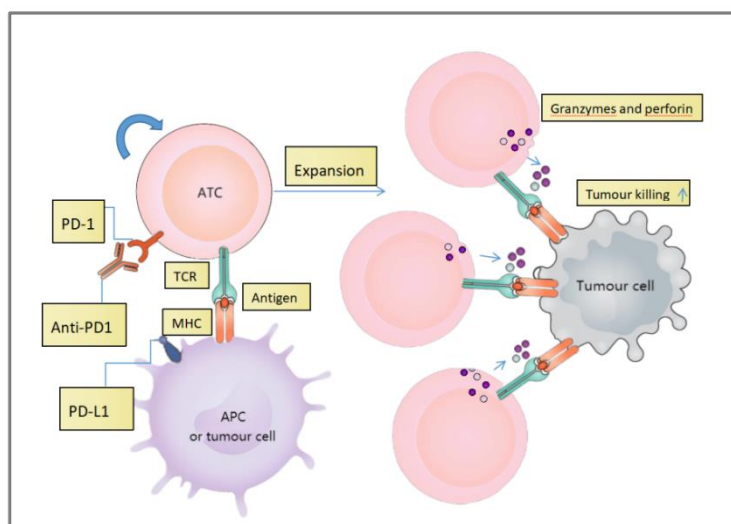


Fig. 1 Mechanisms of PD-1 ICIs [3]

3. The impact of MSI on the efficacy of ICIs

Mismatch repair (MMR) genes play a role in DNA repair pathway, and dysfunctions of these genes products leads to defective MMR. Microsatellites, also known as short tandem repeats, are generally consist of 1~6 nucleotides arranged in tandem and repeated and are prone to mutation because they are small fragments of repetitive structures. MSI refers to the phenomenon of microsatellite length variation caused by defective MMR [4]. According to the difference of MSI expression, CRC can be classified into two categories: MSI-H and MSI-L.

MSI-H CRC cells present more neoantigens on its MHC due to high tumor mutation burden (TMB). Therefore, they are infiltrated by abundant immune cells, characterised by high levels of CD8⁺ tumor infiltrating lymphocytes (TILs), infiltration of T helper 1 CD4⁺ TILs and IFN- γ secretion, showing that MSI-H CRC may be more susceptible to be identified and assaulted by CTLs. In this microenvironment of T-cell inflammation, to escape immune-mediated killing, MSI-H CRC suppresses T-cell activity by upregulating immune checkpoints, such as PD-L1 [2]. Thus, ICIs are more effective to CRC patients with MSI-H (Fig. 2).

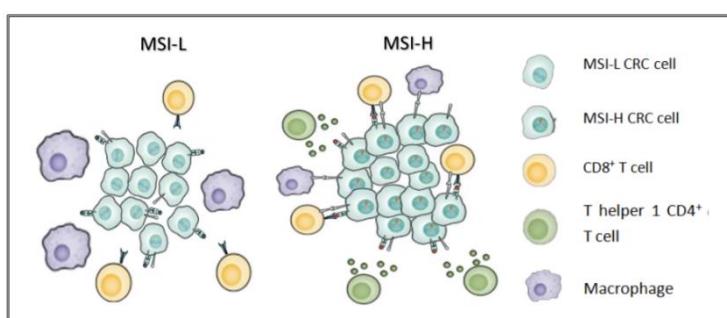


Fig. 2 TME in different MSI CRC [4]

In contrast to MSI-H CRC, MSI-L CRC cells have a low probability of generating immunostimulatory neoantigens, and the tumor microenvironment (TME) contains fewer TILs and more immunosuppressive cells (e.g., regulatory cells) [1]. Therefore, the efficacy of ICIs in MSI-L CRC patients is not satisfactory. In general, the impact of MSI on ICIs' efficacy on ICIs mainly depends on the interaction of immune cell infiltration and tumor cell immunization and escape mechanism (Fig. 2).

4. ICIs combination therapy based on MSI-H CRC secondary drug resistance

4.1. Combination of multiple ICIs

ICIs monotherapy does not block all immune checkpoint pathways or signals, and the combination of multiple ICIs can improve the response rate of ICIs in MSI-H CRC patients. For example, nivolumab combined with ipilimumab (anti-CTLA-4 antibody) improved clinical outcomes in CRC patients with MSI-H [1]. Therefore, the combination of multiple ICIs is considered a potential option for MSI-H mCRC that are resistant to ICIs monotherapy.

4.2. Manipulation of the gut microbiota profile

Study have shown that changes in microbiota composition effectively influence the therapeutic response to ICIs. The sterile or antibiotic-treated mice received faecal microbiota transplantation of cancer patients improved significantly the anti-tumor effect of ICIs [1], suggesting that controlling the distribution of the gut microbiota is considered a promising strategy to enhancement of ICIs efficacy in cancer patients.

5. ICIs combination therapy based on MSI-L CRC primary drug resistance

5.1. ICIs combined with ICD induction agent chemotherapy

It has now been established that immunogenic cell death (ICD) is a way of chemotherapy drugs to induce death of tumor cells. The dead tumor cells induced by ICD release damage-associated molecular pattern to kill tumor cells directly or activate immune cells attacking tumor cells, thereby eventually exerting the efficacy of anticancer drugs in a long time. Relevant studies have verified tumor cells damage-associated molecular pattern, including the membrane calreticulin exposure before apoptosis, the adenosine triphosphate (ATP) secretion, and the cellular high mobility group box protein B1 (HMG-B1) releasing. Among them, the exposure of calreticulin will release associating signals, promoting dendritic cells to phagocyte tumor cells and presenting tumor antigens, thus leading to activation of tumor-specific T lymphocyte. In addition, the ATP releasing from tumor cells causes autophagy, resulting aggregation, digestion and degradation of organelles. As a non-histone chromatin-binding protein, the binding between HMG-B1 and its related receptor on dendritic cells is essential for the activation and the promotion of dendritic cell antigen presentation to T cells [5].

This method increases the efficacy of ICIs in MSI-L patients by increasing TMB and ability of antigen presentation. Firstly, chemotherapeutic drug of ICD inducers can increase the genetic instability of tumor cells, thereby enhancement of TMB and T cells in the TME. Secondly, the special feature of ICD inducers is that the main mechanism of ICD is that the tumor cells are able to up-regulate certain characteristic proteins on its surface after apoptosis stimulated by chemotherapeutic drugs. These characteristic protein molecules are able to induce the maturation and antigen presentation of dendritic cells, eventually activate specific CTLs to kill tumor cells.

PAN02 is a tumour that contains few TILs and is therefore primary resistant to treatment with ICDs. In a study of ICD inducer (OBP-502) monotherapy, PAN02 cells treated with the ICD inducer were able to increase the release of ATP and HMG-B1, and inoculation of treated PAN02 cells into normal mice significantly increased the number of CD8⁺ TILs. In the next study of combining ICD inducers with PD-1 ICIs in PAN02 tumour-bearing mice, the combination therapy significantly inhibited tumour growth and demonstrated more satisfactory efficacy than monotherapy [6]. Therefore, the combination of ICD inducers and ICIs is promising for the therapeutic of CRC patients with MSI-L.

5.2. ICIs combined with anti-angiogenic agents(AAAs)

This approach of anti-angiogenesis converts MSI-L to MSI-H, increasing the antigen presentation on tumor cells and the infiltration of T cells to tumor tissue. The main target of action of AAAs is vascular endothelial growth factor (VEGF), which function mainly is to regulate blood vessel production. In addition, high concentrations of VEGF induce cytotoxic CD8⁺ T cells apoptosis through upregulation of PD-1 expression and recruitment of regulatory cells. AAAs can enhance the effect of ICIs on TME through reducing the hypoxic environment. This change is benefit to activate the body's immune system, thus promoting T-cell and other immune cells infiltration, and increase antigen-presenting ability of tumor cells, thereby strengthening the immune system response. That is, the tumor vasculature can regulate infiltration and activation of immune cells to influence their functions, whereas immune cells can also affect the normalisation of the tumor vasculature, thereby increasing T-cell infiltration [7].

By strengthening the recruitment and induction of immune cell, AAAs can ease the change of the TME from immune-supportive to immune-suppressive. In a phase Ib trial of combination therapy both regorafenib and nivolumab for mCRC, the objective response rate, one-year overall survival and one-year progression-free survival rate were 36%, 68% and 41.8% respectively, including only one patient with MIS-H (n=25) [8]. Although the sample size of the clinical trial is small, it still shows the potential of the combination AAAs and ICIs for the therapeutic of MSI-L CRC patients.

5.3. ICIs combined with bispecific antibodies

The bispecific antibodies consist of a portion that targets the tumor-associated antigen and a portion that binds the effector cell surface antigen. The two CD3⁺ T cell redirection bispecific antibodies catumaxomab and blinatumomab that have been approved for marketing now work by redirecting T cells to tumor-specific killing. CD3 molecules can form TCR-CD3 complexes with TCR, without the need to form MHC-TCR complexes, which act as first signals to induce T cell activation in response to CD28 co-stimulation. Therefore, the CD3 molecule is most common and critical in the process of T cell recognition and immune response [9].

T cells redirection bispecific antibodies that bind to the tumor-associated antigen in one arm and CD3 ϵ subunits in the TCR in the other. When target cell and effector cell are bound by CD3⁺ T cell redirection bispecific antibodies relatively closely, an immune synapse will be formed between the two cells. Synaptic formation leads to TCR crosslinking and T cell activation, leading to pro-inflammatory cytokine release and T cell proliferation induction [9]. This method transforms the MSI-L into MSI-H by increasing infiltration rate of T cells and TCR cross-linking, thereby improving the ICIs' efficacy.

In one study, researchers combined pembrolizumab with blinatumomab B-cell acute lymphoblastic leukemia humanized mice. The combination therapy reduced the probability of developing myeloid minimal residual disease, although blinatumomab and pembrolizumab have shown good results with monotherapy [10].

6. Conclusions

Despite the great success of ICIs in treating MSI-H CRC patients, there are still many issues to be addressed as secondary resistance occurs, as well as a majority of MSI-L CRC patients with primary resistance. Firstly, preclinical MSI biomarker testing in patients is essential as this directly leads to the applicability of ICIs. Second, the mechanism of secondary resistance against MSI-H patients remains to be elucidated. Finally, given the paucity of clinical cases of ICIs in the treatment of MSI-L patients (including combination therapy), a large number of clinical as well as preclinical trials are still needed.

Author Contribution

All the authors contributed equally, and their names were listed in alphabetical order.

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