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ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Oncology*, Marina Senchukova, MD, PhD, Professor, Doctor, Department of Oncology, Orenburg State Medical University, Orenburg 460001, Russia.
masenchukova@yandex.com

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Is the combination of immunotherapy with conventional chemotherapy the key to increase the efficacy of colorectal cancer treatment?

Jonadab E Olguin, Monica G Mendoza-Rodriguez, C Angel Sanchez-Barrera, Luis I Terrazas

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Jonadab E Olguin, Luis I Terrazas, Laboratorio Nacional en Salud, Diagnóstico Molecular y Efecto Ambiental en Enfermedades Crónico-degenerativas, Facultad de Estudios Superiores Iztacala, Universidad Nacional Autónoma de México, Tlalnepantla 54090, Estado de Mexico, Mexico

Monica G Mendoza-Rodriguez, C Angel Sanchez-Barrera, Luis I Terrazas, Unidad de Biomedicina, Facultad de Estudios Superiores Iztacala, Universidad Nacional Autónoma de México, Tlalnepantla 54090, Estado de Mexico, Mexico

Corresponding author: Luis I Terrazas, PhD, Chairman, Senior Scientist, Unidad de Biomedicina, Facultad de Estudios Superiores Iztacala, Universidad Nacional Autónoma de México, Avenida de los Barrios # 1, Tlalnepantla 54090, Estado de México, Mexico.

literrazas@unam.mx

Abstract

Colorectal cancer (CRC) is among the most prevalent and deadly neoplasms worldwide. According to GLOBOCAN predictions, its incidence will increase from 1.15 million CRC cases in 2020 to 1.92 million cases in 2040. Therefore, a better understanding of the mechanisms involved in CRC development is necessary to improve strategies focused on reducing the incidence, prevalence, and mortality of this oncological pathology. Surgery, chemotherapy, and radiotherapy are the main strategies for treating CRC. The conventional chemotherapeutic agent utilized throughout the last four decades is 5-fluorouracil, notwithstanding its low efficiency as a single therapy. In contrast, combining 5-fluorouracil therapy with leucovorin and oxaliplatin or irinotecan increases its efficiency. However, these treatments have limited and temporary solutions and aggressive side effects. Additionally, most patients treated with these regimens develop drug resistance, which leads to disease progression. The immune response is considered a hallmark of cancer; thus, the use of new strategies and methodologies involving immune molecules, cells, and transcription factors has been suggested for CRC patients diagnosed in stages III and IV. Despite the critical advances in immunotherapy, the development and impact of immune checkpoint inhibitors on CRC is still under investigation because less than 25% of CRC patients display an increased 5-year survival. The causes of CRC are diverse and include modifiable environmental factors (smoking, diet, obesity, and alcoholism), individual genetic mutations, and inflammation-associated bowel

diseases. Due to these diverse causes, the solutions likely cannot be generalized. Interestingly, new strategies, such as single-cell multiomics, proteomics, genomics, flow cytometry, and massive sequencing for tumor microenvironment analysis, are beginning to clarify the way forward. Thus, the individual mechanisms involved in developing the CRC microenvironment, their causes, and their consequences need to be understood from a genetic and immunological perspective. This review highlighted the importance of altering the immune response in CRC. It focused on drugs that may modulate the immune response and show specific efficacy and contrasted with evidence that immunosuppression or the promotion of the immune response is the answer to generating effective treatments with combined chemotherapeutic drugs.

Key Words: Colorectal cancer; Immunotherapy checkpoint inhibitors; Chemotherapy; Immunotherapy; Immune response

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Core Tip: This review focused on the drugs that may modulate the immune response and show specific efficacy in the treatment of colorectal cancer. We then presented the evidence that immunosuppression or promotion of the immune response is the answer to generating effective treatments with combined chemotherapeutic drugs.

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INTRODUCTION

The origin of colorectal cancer (CRC) is heterogeneous. The general classification of CRC is divided into inherited, sporadic, and intestinal bowel diseases. Inherited CRC, which represents approximately 5% of all CRC cases, includes either the presence or absence of colonic polyps, such as Lynch syndrome and serrated polyposis syndrome[1]. Sporadic CRC (approximately 70% of CRC cases) is sustained by environmental and modifiable risk factors, including stress, diet, and age. Sporadic CRC has a monoclonal origin and is characterized by mutation accumulation in oncogenes and tumor suppressor genes. The second pathway of CRC includes the traditional APC-KRAS pathway and the microsatellite instability group, both having an essential role in clinical studies[2]. The third pathway includes intestinal chronic inflammatory diseases, such as Crohn's disease and ulcerative colitis, which could result in colitis-associated colon cancer[3].

From a biological perspective, this evidence demonstrates that the origin of CRC is diverse. The response to therapies is not always homogeneous in patients. The best treatment should be based on the tumor's unique characteristics. Effective treatments need to be broad and involve chemical and immunological molecules. The context of the broad causes of CRC development is highly involved in the low effectiveness of either single chemotherapeutics or classical immunotherapy by checkpoints inhibitor (ICI) administration during this oncological pathology. An in-depth and more precise description of the CRC origin and development, including a role for both immune response and inflammation, can be found in[4,5].

CONVENTIONAL TREATMENTS FOR COLON CANCER AND MECHANISMS OF ACTION FROM A GENETIC PERSPECTIVE

CRC is one of the deadliest diseases in the world. Despite advances in diagnosis, treatment strategies remain an essential bottleneck affecting survival, in which the pathological stage represents the most important prognostic factor for patients with CRC. The accurate classification of lesions is the primary tool to decide the most appropriate treatment and therapy[6]. The treatment for early-stage CRC (stage I and stage II) currently consists of resecting the tumor area with regional lymph nodes, which has a 5-year disease-free survival rate of 95%[7]. In the advanced stage of the disease (stages III and above), the rate of disease-free survival drops from 90% to 50% for surgery alone, requiring the administration of

chemotherapeutics, and only 17%-20% of these patients ultimately survive[8,9].

5-Fluorouracil (5-FU) has been central in treating advanced CRC since 1957. Unfortunately, the response rate to 5-FU as the first-line chemotherapy in advanced CRC is still only 10%-15%. In contrast, 5-FU combined with other anticancer drugs as adjuvants, such as leucovorin and oxaliplatin (FOLFOX) or leucovorin calcium and irinotecan, increases the effectiveness of 5-FU by 50%[10,11].

5-FU is the third most commonly used chemotherapeutic agent for the treatment of solid malignancies worldwide[12]. Heidelberger synthesized it in the early 1950s as a derivate of fluoropyrimidines. This drug was one of the first chemotherapeutics reported to have anticancer activity. It was tested in diverse tumors in rats and mice, where it significantly reduced tumor burden. Additionally, tumoral tissues incorporated this compound more rapidly than normal tissues, which pointed to its potential use as a chemotherapeutic drug[13,14]. In 1962, the Food and Drug Administration approved the use of 5-FU for treating CRC.

In intravenous administration, 5-FU is incorporated rapidly into the cells through facilitated transport as uracil[15]. Subsequently, its metabolism can be driven in two ways, *i.e.*, *via* anabolic and catabolic routes, which compete with each other. In sensitive cancerous cells, the anabolic pathway leads to the conversion of this drug into several active metabolites, such as fluorodeoxyuridine monophosphate, fluorodeoxyuridine triphosphate, and fluorouridine triphosphate[16]. The active metabolites interfere with nucleoside metabolism and can be incorporated into RNA and DNA, leading to cytotoxicity and cell death[17,18]. This mechanism is due to its similar structure to pyrimidine, molecules of DNA and RNA, an analog of uracil with a fluorine atom at the C-5 position in place of hydrogen[19]. Fluorodeoxyuridine monophosphate disrupts the function of thymidylate synthase, a key enzyme responsible for providing deoxynucleotide triphosphates, which are necessary for DNA replication and repair, catalyzing the reaction of deoxyuridine monophosphate to deoxythymidine monophosphate synthesis [14,15]. An insufficiency in deoxythymidine monophosphate leads to the depletion of deoxythymidine triphosphate, which perturbs the levels of the other deoxynucleotide triphosphates[16-20] (Figure 1).

5-FU has primarily been used in the treatment of solid cancers of digestive origin, such as colorectal, anal, pancreatic, esophageal, gastric, and ampullary tumors, and less frequently in breast, cervical, and head and neck cancers[21-23]. CRC treatment includes various chemotherapeutic drugs. As the backbone of treatments, 5-FU has been used for more than five decades, and more recently, it has been combined with other chemotherapeutic drugs to potentiate its anticarcinogenic effect[22,24].

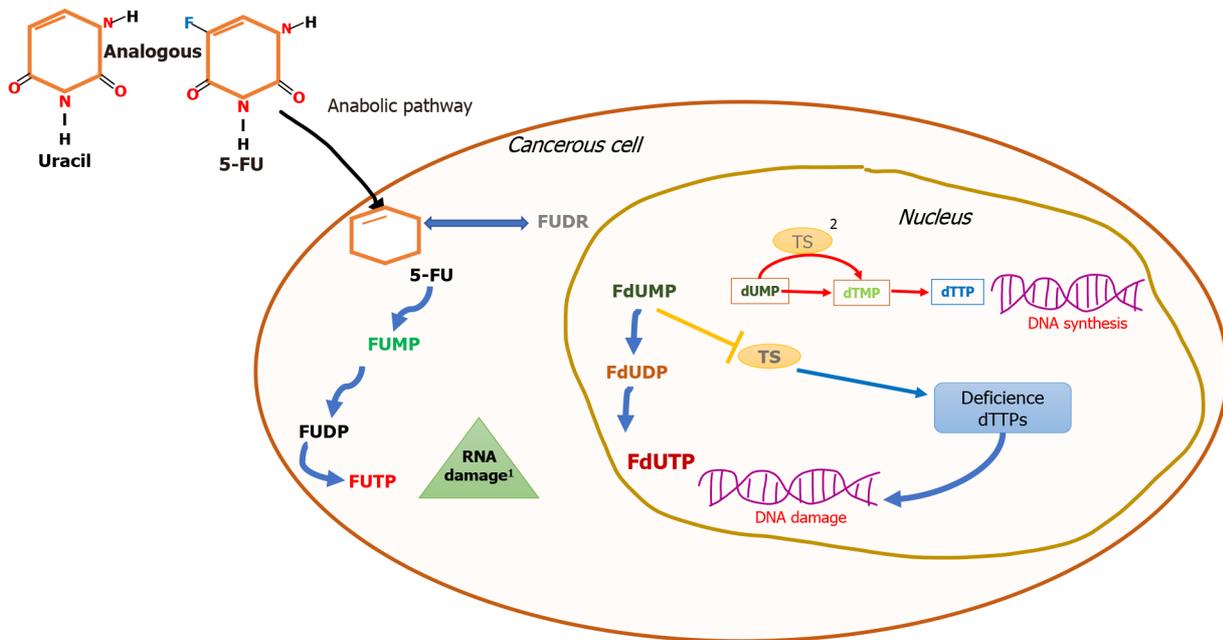
The use of alternative broad-spectrum chemotherapeutics in addition to 5-FU has been proposed for colon cancer treatment. Doxorubicin treatment combined with other drugs, such as metformin and sodium oxamate, reduces the proliferation rate of colon cancer cell lines *in vitro*[25]. However, the use of doxorubicin in patients is limited by the side effects frequently associated with this drug, such as hepatotoxicity, nephrotoxicity, pulmototoxicity, and cardiotoxicity[26,27]. Additionally, doxorubicin can lead to chemoresistance in tumor cells through nuclear factor kappa B translocation to the nucleus and DNA binding because of the damage induced by this drug, triggering the expression of antiapoptotic genes[28].

In CRC, nuclear factor kappa B nuclear translocation is a characteristic in more than 70% of patients, limiting the use of doxorubicin[29]. Another disadvantage of this drug is its anthracycline nature since it is extracted from *Streptomyces spp.* Cancer cells frequently show rapid resistance to naturally occurring cancer drugs, diminishing their effectiveness, whereas they are more sensitive to antimetabolites, such as 5-FU and cisplatin, among others[30]. The use of other chemotherapeutics, such as tamoxifen, which is highly effective and frequently used in breast cancer treatment, has an adverse effect in the treatment of CRC[31]. Due to the molecular characteristics of each type of cancer, the successful use of tamoxifen in breast cancer lies in its mechanism of action. Approximately 80% of all breast cancers are positive for the estrogen receptor, and tamoxifen inhibits the expression of estrogen-regulated genes by the competitive inhibition of this receptor. Different reports indicate that tamoxifen has the opposite effect on CRC, increasing the risk of developing this type of cancer[31,32].

MOLECULAR PERSPECTIVE FOR THE USE OF CHEMOTHERAPEUTIC STRATEGIES IN CRC TREATMENT: WHICH IS THE RIGHT DRUG?

CRC is a molecularly heterogeneous disease in which genetics and cellular events accumulate to endow tumor cells with aggressive characteristics, including chemotherapy resistance. Chromosomal instability, mismatch repair, and methylator phenotype are the three major pathways involved in acquiring tumorigenesis and a malignant phenotype and could be present in sporadic and inherited CRC[33,34]. The choice of better therapy is based on cancer-related features and patient-related factors, such as the number and localization of metastases, tumor progression, presence or absence of biochemical markers, and comorbidity[35-37]. Despite all these characteristics, treatment based on the antineoplastic effects of 5-FU is the cornerstone of therapy in advanced CRC stages.

Treatment with 5-FU in combination with other drugs, such as oxaliplatin (OXA), irinotecan, capecitabine, bevacizumab, cetuximab, panitumumab, ziv-aflibercept, regorafenib, and ramucirumab, increases its effectiveness and has been approved by the Food and Drug Administration for the



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Figure 1 5-Fluorouracil mechanism of action. The 5-fluorouracil structure is analogous to that of the nucleotide uracil; its ability to disrupt standard RNA processing and function is mediated by three primary metabolites: fluorodeoxyuridine monophosphate, fluorodeoxyuridine diphosphate, and fluorouridine triphosphate. ¹: 5-fluorouracil inhibits thymidylate synthase activity by fluorodeoxyuridine monophosphate metabolite binding, blocking the typical substrate deoxyuridine monophosphate that inhibits deoxythymidine monophosphate synthesis leading to deoxythymidine triphosphate imbalance. The consequent result is DNA damage due to a deficiency in its synthesis and its repair; ²: DNA replication and repair are regulated by deoxyuridine monophosphate transition to deoxythymidine monophosphate. This step is coordinated by thymidylate synthase; FUMP: Fluorodeoxyuridine monophosphate; FUDP: Fluorodeoxyuridine diphosphate; FUTP: Fluorouridine triphosphate; dUMP: Deoxyuridine monophosphate; dTMP: Deoxythymidine monophosphate; FUDR: Fluorodeoxyuridine; FdUMP: Fluorodeoxyuridine monophosphate; dTTP: Deoxythymidine triphosphate; FdUDP: Fluorodeoxyuridine diphosphate; FdUTP: Fluorodeoxyuridine triphosphate; 5-FU: 5-Fluorouracil; TS: Thymidylate synthase.

management of CRC[38]. Thus, during stages III or IV in resected CRC patients, the use of combination treatment, such as FOLFOX or 5-FU, leucovorin calcium, and irinotecan, is common as a first-line treatment. This strategy significantly increases the survival rate of these patients[39]. The initial chemotherapy scheme and the decision on better combinatory drugs depends on multiple conditions in the patients. In metastatic CRC limited to the liver or lung, surgery and the rapid initiation of chemotherapy appears to be the best option. When CRC cure is not possible, three additional scenarios can arise: (1) Patients with advanced tumors and symptoms require rapid tumor shrinkage to provide palliation, which begins with chemotherapy; (2) Asymptomatic patients with bulky tumor and possible rapid progression are likely to become symptomatic in a short period; and (3) Patients without symptoms but disseminated disease who never had resectable disease but whose tumors remain non-bulky are likely to remain asymptomatic for an extended period. In the last two scenarios, the initiation of chemotherapy can be discussed[22,40]. Previous work in the Nordic population demonstrated that early treatment with 5-FU plus leucovorin in asymptomatic patients with advanced CRC prolonged survival and delayed both disease progression and the onset of symptoms[41]. In another study in Australasian and Canadian populations of asymptomatic patients using the same chemotherapy regimen, no difference was reported between early or delayed chemotherapy use until symptoms appeared[42]. Thus, clinical treatment requires a medical discussion and the patient’s preference when cure is not possible. The spectrum of molecular alterations that offer alternative management for this disease could be explored.

Alterations in genes related to survival, angiogenesis, proliferation, and apoptosis incorporate additional strategies into CRC treatment. The *RAS*, *KRAS*, and *NRAS* genes play an essential role as prognostic and predictive indicators in CRC treatment[43-45]. Mutations in the DNA at position 12 in the *KRAS* protein are significantly associated with a poor prognosis: a 5-year survival rate of approximately 3%[46]. Patients with this mutation are not candidates to receive treatment with monoclonal antibodies, such as cetuximab or panitumumab, which target the epidermal growth factor receptor (EGFR)[47-50]. Blocking EGFR represents the second line of treatment in patients with wild-type *RAS* together with the backbone 5-FU, leucovorin calcium, and irinotecan therapy. Therefore, the patient’s genetic and tumor-specific factors need to be considered when choosing chemotherapeutic and combination schemes to avoid resistance and undesired responses to these therapies.

Drug resistance and consequent therapy failure are the main problems clinicians face in treating different neoplasms, which limit the quality of life and long-term remission rates as a consequence of tumor growth and spreading leading to 90% of patients dying [51,52]. Drug resistance is a highly complex process that is commonly classified into two types: intrinsic and acquired. Both types of drug resistance lead to the regulation of molecular mechanisms of chemoresistance, such as the activation of transporter pumps, oncogenes, tumor suppressor genes, mitochondrial alteration, DNA repair, autophagy, epithelial-mesenchymal transition, cancer stemness, and exosomes [53,54].

In the intrinsic phenotype, diverse alterations existing before drug administration in the patient complicate the selection of chemotherapy. The inherent genetic mutations in tumors, such as a *KRAS* mutation in exon 2 in codon 12 or 13, are the most frequent mutations associated with poor prognosis and drug resistance in CRC [55,56]. Therapies based on the first line of treatment using FOLFOX or 5-FU, leucovorin calcium, and irinotecan plus cetuximab or panitumumab (anti-EGFR) are ineffective in patients with *KRAS* mutations [57]. Recent studies indicate that mutations in genes related to the pathways that regulate tumor cell survival and proliferation and inhibit apoptosis in tumor cells, such as *AKT1* and *CTNNB1*, contribute to 5-FU chemotherapeutic resistance in CRC. The *CTNNB1* gene encodes the β -catenin protein, which plays a crucial role in cancer by activating the Wnt/ β -catenin signaling pathway. This pathway is associated with tumorigenesis and CRC resistance, and it upregulates genes and proteins, such as multidrug resistance gene (*MDR1*) and inhibitor of apoptosis (*Bcl2*), to induce epithelial-mesenchymal transition and regulate the tumor microenvironment (TME) [58-60].

IS CHEMOTHERAPY AN INDUCER OF IMMUNOSUPPRESSION IN CRC?

The heterogeneity of tumors, including CRC, consists of heterogeneity in cancer and infiltrated resident host cells, extracellular matrix, and immune and inflammatory cells, such as macrophages, dendritic cells, myeloid-derived suppressor cells, T cells, mast cells, and natural killer cells. These components comprise the TME, which has a dynamic composition [61]. It is well known that one of the main functions of the TME is to provide a protective function for tumor cells, inducing crosstalk between immune and nonimmune cells that leads to tumor-mediated immunosuppression, supporting tumor growth and survival [62]. Recent reports indicate that the TME in CRC contributes to cancer progression and drug resistance through high interstitial pressure, fibrosis, and the degradation of the therapeutic agent by enzymatic activity and inducing immunosuppression [61,63,64]. These findings indicate that the regulation of immune cells surrounding the tumor has a critical role in the response to therapies for CRC. Thus, chemotherapy and immunotherapies targeting the recovery activity of immune cells are likely necessary to fight CRC.

The study of the effect of chemotherapeutic drugs on immune cells is controversial. The central concept here is that chemotherapy reduces the capacity of the immune system to function, but how could a drug affect the capacity and efficiency of the immune response to induce an efficient post-treatment response? Perhaps the "original" concept has a flawed approach. Evidence suggests that after 5-FU treatment in a mouse model, bone marrow cellularity decreases, but platelets and thrombopoietin, which are close to the immune response, rebound [64,65]. Similarly, the serum of patients diagnosed with stage III/IV CRC who had received FOLFOX chemotherapy showed increased levels of heat shock protein 70, which belongs to the damage-associated molecular patterns recognized by innate receptors [66]. Later, *in vitro* studies showed that the supernatants of dying CRC cells treated with OXA and 5-FU induced a mature phenotype in dendritic cells coexpressing HLA-DR, CD80, and CD86 and producing interleukin-1 β , tumor necrosis factor- α , and MIP-1 α in a TLR-4-dependent manner [66]. These results strongly suggested that OXA/5-FU treatment induced the activation of the innate immune response during CRC. Additionally, increased numbers of myeloid-derived suppressor cells have been reported in a mouse model of thymoma, and treatment with 5-FU combined with gemcitabine selectively induced apoptosis in myeloid-derived suppressor cells. Consequently, increased antigen-specific CD8+ T cells produced more interferon- γ , generating a T cell antitumor response (Figure 2) [66].

Conversely, high levels of the chemokine CCL20 recruit regulatory T (Treg) cells in CRC patients resistant to FOLFOX [67]. However, in blood samples from metastatic FOLFOX-sensitive CRC patients, a reduced percentage of Foxp3+ Treg cells was recorded after treatment [68]. Therefore, the increase in Treg cells is associated with 5-FU chemoresistance. Thus, evidence of 5-FU chemotherapy suggests a role in the specific and direct reduction of suppressive immune cells during CRC. Additionally, the increased apoptosis-induced death of tumor cells by 5-FU could increase the ability of immune cells to recognize damage-associated molecular patterns released by these dying tumor cells, inducing protective inflammation. Evidence needs to be accumulated in this field to clarify whether chemotherapy may be an inducer of immune cell activation (Figure 3).

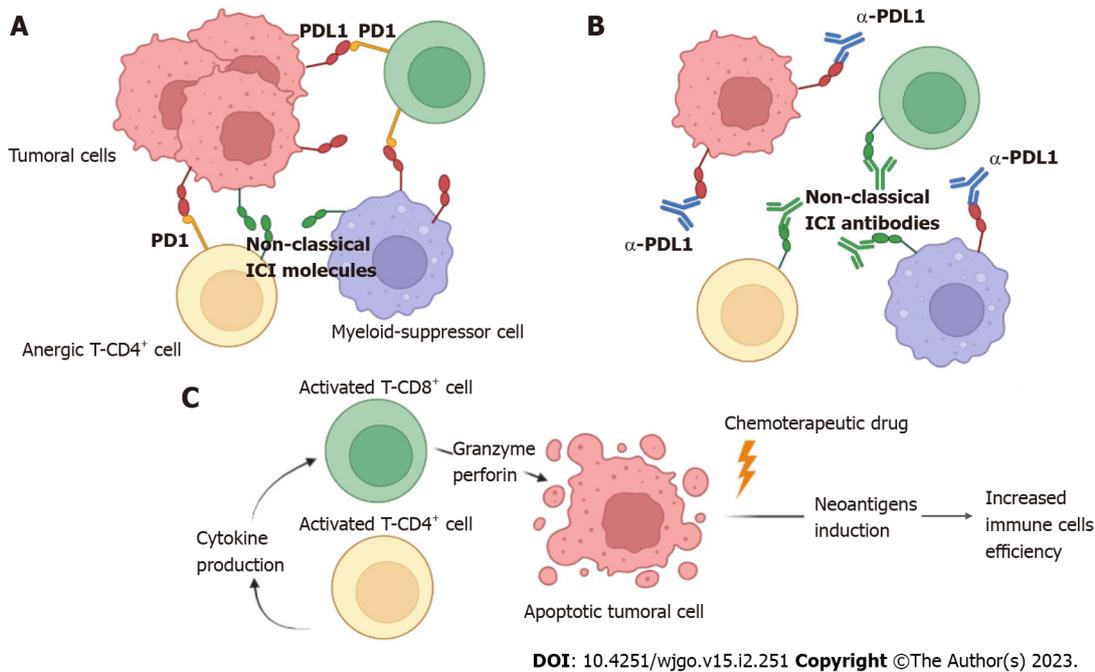


Figure 2 Mechanism of action using either anti-programmed cell death ligand 1 or anti-nonclassical immune checkpoint inhibitor antibodies to increase the effector immune response in colorectal cancer. A: The programmed cell death ligand 1 molecule expressed on both tumor and myeloid suppressor cells interacts with programmed cell death 1 molecules expressed on exhausted CD8⁺ and CD4⁺ T cells, inducing a state of anergy. Additionally, other nonclassical immune checkpoint inhibitor molecules can induce anergy in T cells; B: Anti-programmed cell death ligand 1 antibodies block the interaction of the programmed cell death 1/programmed cell death ligand 1 axis, favoring the return from the state of anergy to exert the effector function of CD4⁺ and CD8⁺ T cells, favoring the reduction of the tumor burden. Most likely, nonclassical immune checkpoint inhibitor antibodies may have a similar effect; C: Once CD4⁺ T cells are activated, they produce cytokines for the efficient activation of CD8⁺ T cells, which in turn produce granzyme and perforin, inducing apoptosis in tumor cells. The addition of chemotherapeutic drugs increases the induction of neoantigens, favoring immune response activation. PDL1: Programmed cell death ligand 1; PD1: Programmed cell death 1; ICI: Immune checkpoint inhibitor.

CLASSICAL ICIS USED AS MONOTHERAPY DURING CRC

The effectiveness of ICI as an immunotherapy treatment has been evaluated in the last decade. The efficacy of these agents is evident in liquid tumors, such as melanoma, leukemia, and solid non-small cell lung carcinoma. Classical ICIs used to treat these oncological pathologies are anti-programmed cell death 1 (PD1), anti-programmed cell death ligand 1 (PDL1), and anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA4) monoclonal antibodies, where anti-CTLA4 has a lower clinical efficacy[68,69] (Table 1).

Diverse reports suggest single or combined therapy using different antibodies targeted against the same or another molecule. In melanoma therapy, nivolumab, a human immunoglobulin G4 anti-PD1 pathway monoclonal antibody, results in an overall survival (OS) rate of 72.9%, whereas the antineoplastic chemotherapeutic dacarbazine resulted in a survival rate of 42.1%[69]. In metastatic melanoma refractory to chemotherapy, treatment with ipilimumab, an anti-CTLA4 antibody, shows high efficacy when combined with anti-PD1 antibodies (either pembrolizumab or nivolumab)[70]. Additionally, nivolumab and ipilimumab combination treatment prolongs progression-free survival, mainly in patients with tumors testing positive for PDL1 expression[71]. Although *in vitro* studies suggested that atezolizumab, avelumab, and durvalumab, all anti-PDL1 antibodies, more effectively block PD1/PDL1 signaling (Figure 2)[72], evidence of the use of an anti-PDL1 antibody as a single approved treatment without immunotherapy or chemotherapy combination is insufficient to conclude their role in inducing protection in metastatic melanoma[73]. Immunotherapy with the anti-PDL1 antibody atezolizumab has been approved to treat non-small cell lung carcinoma combined with chemotherapy, and anti-PDL1 has been approved to treat triple-negative breast cancer[74,75]. Therefore, increased PDL1 expression in the TME of melanoma patients is an efficient marker to predict response to anti-PD1 treatments, which must be applied in all types of cancer when this immunotherapy is suggested[76].

Notwithstanding the successful use of immunotherapy in the neoplasms mentioned above, few reports show an influential role for classical monoclonal ICI using anti-CTLA4 and anti-PD1/PDL1 axis antibodies in CRC. Most clinical assays were disappointing. For example, tremelimumab, a human immunoglobulin G2 anti-CTLA4 antibody, did not produce clinically meaningful results when it was used as a monotherapy in patients with refractory metastatic CRC[77] (Table 1).

Table 1 Types of immune checkpoint inhibitor antibodies used as monotherapy, combined immune checkpoint inhibitor, and immune checkpoint inhibitor + chemotherapy in colorectal cancer

Antibody name	Isotype	Target molecule	Effectiveness ¹ as monotherapy	Effectiveness as combined ICI	Effectiveness as ICI + chemotherapy	Ref.
Ipilimumab	IgG1	CTLA4	Yes	Well tolerated in combination with nivolumab	No	Suzuki <i>et al</i> [80], 2021; Lenz <i>et al</i> [86], 2022; Cohen <i>et al</i> [90], 2020
Tremelimumab	IgG2	CTLA4	No	Yes, durvalumab improved OS and increased lymphoid response	Combined with durvalumab + fluoropyrimidines, oxaliplatin, irinotecan, showed increased OS	Chung <i>et al</i> [77], 2010; Kanikarla Marie <i>et al</i> [85], 2021; Chen <i>et al</i> [102], 2020
Nivolumab	IgG4	PD1	Well tolerated	Well tolerated in combination with low ipilimumab dose, with increased OS	Yes	Overman <i>et al</i> [78], 2017; Kawazoe <i>et al</i> [79], 2021; Lenz <i>et al</i> [86], 2022; Morse <i>et al</i> [87], 2019
Pembrolizumab	IgG4	PD1	Well tolerated, increased OS	No	There is no evidence	Haag <i>et al</i> [82], 2022
Atezolizumab	IgG1	PDL1	There is no evidence	There is no evidence	Safe when combined with cobimetinib, having no effect on OS. Combined with FOLFOX and bevacizumab showed increased progression-free survival, but adverse events were shown	Eng <i>et al</i> [91], 2019; Antoniotti <i>et al</i> [94], 2022
Avelumab	IgG1	PDL1	Increased OS but adverse events were shown	There is no evidence	Combined with cetuximab showed increased T cell killing	Haag <i>et al</i> [82], 2022; Stein <i>et al</i> [97], 2021
Durvalumab	IgG1	PDL1	Increased progression-free survival, but adverse events were shown	There is no evidence	Safe when combined with MEKi, having no effect on OS	Oh <i>et al</i> [84], 2022

¹Effectiveness was considered as increased survival, well tolerated treatment in patients, or simply a lack of side effects associated with the treatment.

IgG: Immunoglobulin G; OS: Overall survival; PDL1: Programmed cell death ligand 1; PD1: Programmed cell death 1; CTLA4: Cytotoxic T-lymphocyte-associated protein 4; ICI: Immune checkpoint inhibitor; FOLFOX: 5-FU therapy with leucovorin and oxaliplatin; MEKi: Inhibitor of MAPK/ERK kinase.

Another monotherapy treatment using nivolumab in CRC patients with microsatellite instability and FOLFOX chemoresistance showed excellent control of the disease, and patients tolerated this treatment well[78]. CRC patients treated with nivolumab combined with an oral heat shock protein 90 inhibitor showed safety profiles and antitumor activity associated with reduced activity of Treg cells and better response of tumor-infiltrating lymphocytes[79]. Interestingly, a report of a woman treated with nivolumab for melanoma with no hereditary CRC background developed colon carcinoma after 7 years of anti-melanoma treatment. The medical service then decided to switch the treatment to ipilimumab, and after four cycles of monotherapy, the colon tumor was in complete remission[80]. Pembrolizumab used as monotherapy in either microsatellite instability-high or mismatch repair-deficient CRC patients produced improvements in health-related quality of life compared to patients treated with leucovorin, 5-FU, and OXA[81]. In one study of refractory mismatch repair, CRC patients treated with pembrolizumab as monotherapy plus maraviroc, an agonist of CCR5 that promotes the activation and recruitment of macrophages inducing immune cell infiltrate in tumors, showed a beneficial toxicity pattern. The OS was higher than expected[82].

ICI with avelumab monotherapy in unresectable metastatic CRC patients who failed FOLFOX chemotherapy showed an OS of 72.2% at 8.1 mo, which was similar to the effect of ICI monotherapy using either pembrolizumab or nivolumab. However, some patients showed treatment-related adverse events[83]. Durvalumab used as monotherapy in microsatellite-instability high/mismatch repair-deficient metastatic CRC patients whose disease had progressed after chemotherapy showed efficiency and a satisfactory progression-free survival of 58.2%; however, side effects were found in 36.4% of patients[84].

Taken together, these results suggest that contrary to anti-CTLA4, ICI monotherapy blocking the PD1/PDL1 axis has a better effect in high microsatellite instability/mismatch repair-deficient metastatic CRC patients who previously displayed chemoresistance. Additionally, combining ICI PD1/PDL1 monotherapy with either antibodies or immune cell stimulators improves treatment efficacy. However, only a small number of clinical trials show increased OS (Table 1). Most likely, the TME reduces the access of ICI antibodies to the target molecules expressed in either immune or epithelial cells (Figure 3).

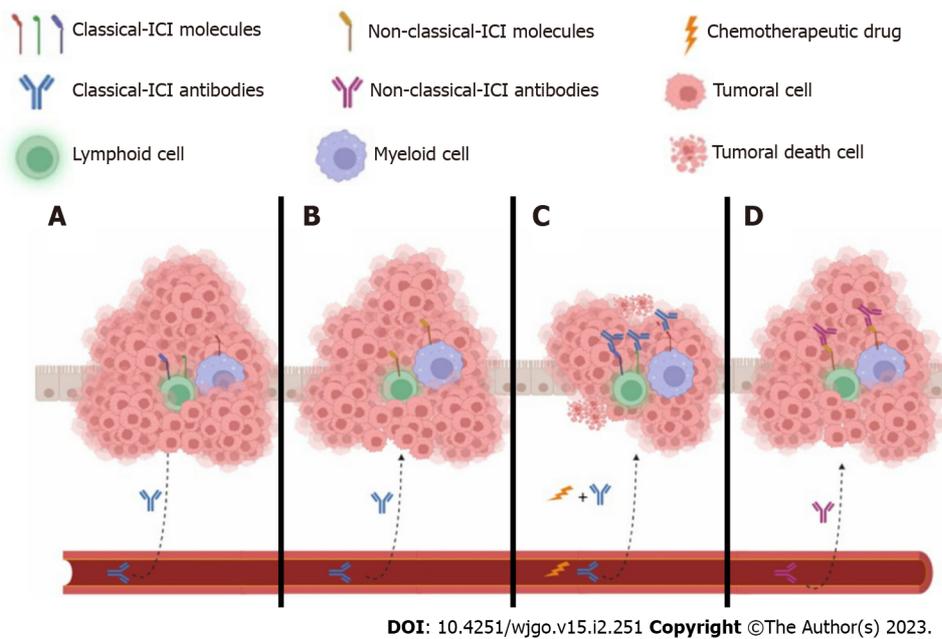


Figure 3 The tumor microenvironment favors or does not allow the access of both classical and nonclassical immune checkpoint inhibitors to their targets in immune cells. A: The classical immune checkpoint inhibitor (ICI) antibody cannot access its target because immune cells are surrounded by tumor cells, although immune cells may express classical ICIs; B: On the other hand, classical ICIs probably have access to immune cells but may not express the targeting molecules; C: Chemotherapy can induce the death of tumoral cells, favoring the formation of neoantigens that may reactivate immune cells. Additional classical ICI antibodies target individual molecules such as cytotoxic T-lymphocyte-associated protein 4, programmed cell death 1, and programmed cell death ligand 1; D: Finally, immune cells expressing nonclassical ICIs could have effector profiles such as helper T type 1 cells, cytotoxic T cells, M1, or N1 when nonclassical antibodies target them. Additionally, tumor epithelial cells may likely express both classical and nonclassical ICIs. ICI: Immune checkpoint inhibitor.

DOES COMBINED IMMUNOTHERAPY INCREASE THE EFFECTIVENESS OF TREATMENT FOR CRC?

Little evidence of the apparent effect of ICI monotherapy on CRC development is available. Conversely, increasing evidence suggests a better outcome using combined ICI, *i.e.*, the use of two monoclonal antibodies targeting CTLA4 or the PD1/PDL1 axis. To improve the immune response, combination treatment with tremelimumab and durvalumab was used in patients for the preoperative management of resectable CRC and liver metastases. These patients improved their OS to 24.5 mo; interestingly, their CD4⁺, CD8⁺, and B cells displayed an activated profile[85]. Additionally, first-line treatment consisting of nivolumab plus low-dose ipilimumab treatment in patients with microsatellite instability and metastatic CRC without previous chemotherapy showed that this combination was well tolerated at the primary endpoint, with robust and durable clinical benefit. However, the study is ongoing, and OS data are not yet available[86]. Previous ICI studies using similar inclusion criteria and antibody doses showed that follow-up over 12 mo of combined treatment resulted in an 85% OS[87]. Recently, the combined use of ipilimumab plus nivolumab before surgery in either mismatch repair-deficient or mismatch repair-proficient CRC patients induced an antitumoral response associated with a lack of signs of cancer after surgery with increased infiltration of CD8⁺PD1⁺ cells; the authors suggested that this combined ICI therapy may be the standard treatment for mismatch repair-deficient CRC patients [21].

Additionally, circulating tumor DNA detection in the blood of patients with durable and ongoing responses to ipilimumab plus nivolumab could be used as a monitoring response and dynamic marker of this combined ICI treatment[88,89]. Finally, a study attempted to analyze whether pseudo progression was observed in mismatch repair-deficient CRC patients treated with nivolumab plus ipilimumab, showing that this treatment rarely induces and confirming a high disease control rate of 86%[90]. Taken together, this evidence strongly suggests that the combined ICI blockade of CTLA4-PD1/PDL1 in mismatch repair-deficient CRC patients is highly successful. However, these patients represent only a tiny fraction of all CRC-diagnosed patients. Therefore, more clinical trials must be developed to obtain sufficient evidence to conclude the positive effects of the classic ICI combination.

USE OF EITHER MONOTHERAPY OR COMBINED IMMUNOTHERAPY PLUS CHEMOTHERAPY TO INCREASE THE EFFECTIVENESS OF TREATMENTS FOR CRC

The combined use of atezolizumab plus aobimetinib, a MAPK/ERK kinase 1 and 2 inhibitor that increases CD8⁺ cell infiltration in tumors of patients with microsatellite-stable metastatic CRC, showed no improvement in OS and was consistent with the safety of using both drugs[91] (Table 1). A similar effect showing only acceptable tolerance to this treatment was observed with durvalumab plus inhibitor of MAPK/ERK kinase in microsatellite-stable metastatic CRC patients[89]. No improved OS was observed using atezolizumab combined with cobimetinib in metastatic CRC patients[92]. A multicenter phase I/II study in June 2017 aimed to analyze the role of durvalumab plus tremelimumab combined with FOLFOX chemotherapy in patients with metastatic CRC, expecting a 6-mo progression-free survival of over 70.7%; however, the authors do not have the final results to date[93].

Recently, the combination of atezolizumab with FOLFOX chemotherapy plus bevacizumab (monoclonal anti-vascular endothelial growth factor antibody) in mismatch repair metastatic CRC patients induced a median progression-free survival of 13 mo, while FOLFOX plus bevacizumab alone resulted in 11 mo of progression-free survival, suggesting that the addition of atezolizumab improves progression-free survival. However, 42% of patients showed neutropenia, and 27% displayed severe adverse events[94]. The same treatment consisting of atezolizumab combined with FOLFOX plus bevacizumab was used in patients with untreated unresectable metastatic CRC, showing no improvement in OS and safety signals[95]. The use of the anti-EGFR antibody cetuximab plus avelumab for treating wild-type *RAS* metastatic CRC patients was safe; the authors suggested that an analysis of circulating DNA in plasma could be an indicator of the positive effects of this treatment. However, the data are insufficient to show the impact on the OS rate[96].

Treatment with cetuximab plus the ICI avelumab in microsatellite stable metastatic CRC patients showed that subclones of tumors expressing PDL1 mutations mediated the resistance to direct avelumab antitumor effects but also increased T cell killing[97]. An analysis of the neutrophil-to-lymphocyte ratio in the blood of chemorefractory metastatic CRC patients treated with cetuximab plus avelumab showed that a high neutrophil-to-lymphocyte ratio was a poor prognostic factor. Thus, the neutrophil-to-lymphocyte ratio could also be a predictor for the effectiveness of the combined ICI cetuximab plus avelumab[98].

Regorafenib, an inhibitor of protein kinases in tumor angiogenesis used in combination with avelumab in microsatellite stable CRC patients, showed increased infiltration of CD8⁺ T cells associated with better outcomes, with an OS of 10.8 mo[99]. Metastatic CRC patients who previously received two radiotherapies and who were treated with durvalumab plus tremelimumab before the third round of radiotherapy showed increased circulating, differentiated, and proliferating CD8⁺ T cells, but the authors concluded that this finding does not meet the prespecified endpoint criteria to consider this combined ICI plus radiotherapy worthwhile for further study; specifically, the authors suggested an objective response rate of at least 25%, but they only obtained a response rate of 8.3%[100].

The addition of FOLFOX-based chemotherapy to avelumab plus an adenovirus vector vaccine capable of inducing a CD4⁺/CD8⁺ T cell response in mismatch repair-deficient microsatellite instability-high metastatic CRC patients showed no improvement in progression-free survival[101]. However, The Canadian Cancer Trials Group suggests that combining tremelimumab and durvalumab to treat patients with high microsatellite instability who had previously received chemotherapy (fluoropyrimidines, OXA, irinotecan, and others) may prolong OS. They correlated the increased effectiveness of this immunotherapy combination with the tumor mutation burden elevated in plasma[102].

It is essential to mention that some research about the combination of chemotherapy and ICI is under development[93]. For example, a phase II trial in 2020 will show whether atezolizumab combined with OXA, radiotherapy, and bevacizumab may increase progression-free survival in microsatellite instability CRC patients[103]. Additionally, in microsatellite instability-high metastatic CRC patients with deficient mismatch repair, a study is currently underway to prove the improvement of disease-free survival by ICI with avelumab plus fluoropyrimidine; the authors suggested that this ICI plus chemotherapy treatment would improve the expected 3-year disease-free survival rate by 12%[104]. Evidence showing that combining ICI with chemotherapy improves treatment efficacy continues to accumulate.

Most clinical trials reported here are recent, and perhaps the evidence is insufficient to conclude that a treatment criterion has already been established. Consequently, evidence supports the hypothesis that the use of classical ICIs improves chemotherapy treatment, mainly in CRC patients with high microsatellite instability. It is crucial for patients who do not have a good prognosis with chemotherapy alone to have a better response with the combination of classical ICI antibodies.

MULTIOMICS, INDIVIDUALIZED IMMUNOTHERAPY, ADOPTIVE TRANSFER OF “TRAINED” IMMUNE CELLS, AND NONCLASSICAL ICIS ARE A NEW HOPE FOR CRC

In recent years, mechanisms have begun to be developed to understand and explain why, in some cases, classical immunotherapy is sufficient to generate benefits in some patients. Multiple factors participate in the development of any pathology, such as the patient's clinical history, genetics, and the ability of their immune cells to act during cancer. We emphasize the importance of the recruitment of immune cells to the TME; in the case of melanoma, non-small cell lung cancer, and leukemia, the capacity of the immune cells to access is greater, which together with ICIs increases the bioavailability of monoclonal antibodies to find the antigens expressed in the required enclosures to be detected and removed or blocked[105]. In contrast, other types of oncological pathologies are available when access to the tumor site is more difficult for both immune cells and classical ICI antibodies, such as CRC[106]. In addition, the causes of CRC are multiple, and we cannot attempt to generalize a unique treatment for all varieties of CRC to reduce the statistics of this oncological pathology on the rise.

The single-cell multiomics technique has shed light on the complexity of the individual immune response elicited against any agent. This approach facilitates the individual characterization of groups of cells by identifying the gene transcripts at a specific time[107]. This technique depends on the efficiency of flow cytometry to distinguish and separate individual cells, the equipment used to amplify mRNA transcripts and synthesize complementary strand DNA, and sequencing equipment, allowing for robust data with high precision and certainty[108]. The advancement of these latest-generation technologies allows not only the expression of the classic ICI (CTLA4, PD1/PDL1) to be distinguished but also the characterization of mRNA transcripts in specific immune or epithelial cell populations at a particular time. These transcripts, already expressed as proteins, can individually be proposed as new nonclassical ICIs in patients[109], generating a wide range of therapeutic targets that, as in the case of CRC, increase the efficiency of previous treatments.

Some surface molecules involved in suppressive functions for activated T cells, Treg cells, macrophages, neutrophils, and epithelial cells have been proposed as immunotherapy targets. Glucocorticoid-induced tumor necrosis factor receptor-related protein (GITR), T cell immunoglobulin and mucin domain 3 (TIM3), LAG3, CD39, CD73, CD47, and SIRP-1 α (a do not eat me signal)[110] warrant evaluation as monotherapy or combined therapy in CRC.

TIM3 is an overexpressed inhibitory receptor in active immune cells, including myeloid and lymphoid cells, with suppressive and modulatory characteristics. It is relevant in reducing interferon- γ production by helper T type 1 cells after binding to its ligand, galectin-9[111]. TIM3 is also overexpressed by Treg cells in a colitis-associated colon cancer mouse model[112]. The combination of TIM3 with anti-PD1 ICI antibodies is a good prospect in a murine breast cancer model[113]. Sabatolimab, an anti-TIM3 antibody, has already been used as a treatment in ovarian, CRC, and non-small cell lung cancer combined with an anti-PD1 antibody, being well tolerated and improving antitumor activity [114]. GITR has a role in the immunomodulation of effector T cells and increases tumor resistance[113, 115]. Treatment with an anti-GITR antibody combined with pembrolizumab improves the disease control rate compared with anti-GITR used as monotherapy for treating CRC, melanoma, and adrenal carcinoma[116].

Lymphocyte activation gene-3 (LAG3 or CD223) has a structure similar to that of the CD4 molecule, joining major histocompatibility complex II in antigen-presenting cells. However, two of their immunoglobulin-like domains can bind receptors in tumor cells[81]. Blockage of LAG3 induces increased interleukin-2 production and enhances T cell proliferation[117]. Therefore, LAG3 has been proposed as an ICI; the genes *LAG3* and *IDO1* were shown to be overexpressed in a phase II study of pembrolizumab use as ICI monotherapy in patients with esophageal squamous cell carcinoma. The authors suggested that a combination of ICIs is needed to induce immunity against this tumor[118]. CD73 is an extracellular adenosine receptor expressed in immunosuppressant cells (such as Treg cells), favoring tumor progression[119].

Recently, single-cell RNA sequencing in a colitis-associated CRC murine model showed that an anti-CD73 antibody has a significant role in improving the anticancer functions of Treg cells, and exhausted CD8⁺ T cells became activated CD8⁺ T cells. In contrast, anti-PD1 antibodies in the same model depleted Treg cells and M2 macrophages[120], suggesting a synergistic role for the new ICI anti-CD73 that may improve the positive effects of anti-PD1 monotherapy. *Ex vivo* samples of blood and tumors from microsatellite instability CRC patients showed that atezolizumab alone could reactivate T cells.

Furthermore, adding tiragolumab, an anti-TIGIT antibody, restored intraepithelial CD4 T and CD8 T cell function by favoring interferon- γ and tumor necrosis factor- α production[120,121]. TIGIT is a receptor upregulated in natural killer and activated T cells when the modulation of their effector abilities is necessary for the microenvironment, such as cancer. It is also overexpressed in Treg cells [122]. The use of avelumab plus the adoptive transfer of autologous dendritic cell vaccine in chemotherapy-treated mismatch repair-proficient metastatic CRC patients had a successful result because this treatment was well tolerated. Furthermore, treatment was terminated early because 11% of patients were disease free at 6 mo, and progression-free survival was increased by 40% [123]. This evidence also suggests that new ICI research could open other possibilities for specific and beneficial

treatment for CRC patients because either immune or epithelial cells may express nonclassical ICI molecules (Figure 2).

CONCLUSION

Chemotherapy using 5-FU remains the primary treatment for CRC, despite its high toxicity and low efficacy. New strategies targeting ICIs have been useful in some oncological pathologies; however, evidence showing the effectiveness of classical ICI monotherapy in CRC is scarce. A combination of classical ICI antibodies targeting CTLA4 and PD1/PDL1 molecules showed stronger efficacy for CRC treatment. Finally, classical ICI plus conventional chemotherapy is effective, as evidenced by increased OS, but these strategies are not yet well established, and some clinical studies are ongoing. Evidence suggests that chemotherapy produces neoantigens, increasing tumor immunogenicity that may activate immune responses[124]. This increased immunogenicity is likely the reason for a better response when classical ICI plus chemotherapy is used and may represent a pathway to design new therapeutic strategies aimed at improving the response in CRC patients based on immunological reactivation combined with conventional chemotherapy. Knowledge of the TME in CRC is essential to understand immunosuppression. New options for nonclassical ICIs obtained by single-cell sequencing are shedding light on this area and will probably improve the effectiveness of many treatments.

We are possibly on the verge of major findings in the study of CRC, where the immune response will continue playing a leading role and where new proposals with nonclassical ICIs may reduce the current statistics and poor prognoses for this oncological pathology.

FOOTNOTES

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Country/Territory of origin: Mexico

ORCID number: Luis I Terrazas 0000-0003-4649-4117.

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