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REVIEW

Current status of immunotherapy in metastatic colorectal cancer

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Abstract

Background Immunotherapy focuses on selectively enhancing the host's immune response against malignant disease. It has been investigated as an important treatment modality against malignant disease for many years, but until recently its use was mostly limited to a few cancers. The advent of new immunemodulating agents in the recent past has changed the landscape for management of many solid tumors. Currently, immunotherapy offers a valuable, and in many cases, a more effective alternate to the conventional cytotoxic therapy. Colorectal cancer is a leading cause of cancer-related death. Despite progress in systemic therapy, most patients with metastatic colorectal cancer die of their disease. There is an unmet need for more effective treatments for patients with metastatic colorectal cancer. The current data support that colorectal tumors are immunoresponsive and a subset of patients with advanced disease achieve long term benefit with immunotherapy.

Objectives This review aims to provide the current status of immunotherapy in patients with metastatic colorectal cancer.

Methods We researched sources published in the English language between January 2000 and August 2018 and listed within the PubMed database using combinations of the key words and reviewed the proceedings of international cancer conferences and current guidelines made by major cancer societies.

Results In this review, we summarize the current status of research on immunotherapy in metastatic colorectal cancer and discuss various treatment modalities including checkpoint inhibitors, cancer vaccines, adoptive cell transfer, oncolytic virus therapy, and various other agents that are under investigation with a special emphasis on immune checkpoint inhibitors. Since the toxicity profile of immunotherapy is very different from conventional cytotoxic agents and could involve any organ system, we briefly review common adverse effects and their management.

Keywords Immunotherapy · Metastatic colorectal cancer · Immune checkpoint inhibitors · Cancer vaccine

Introduction

The field of immunotherapy is a growing domain in oncology. Over the past few years, the arrival of several novel immune-modulating antibodies has revolutionized the approach of cancer treatment in various solid tumors. Colorectal cancer (CRC) is one of the leading causes of cancer-related death in the Western countries. Close to every third patient diagnosed with colorectal cancer either presents with, or develops, metastatic disease [1, 2]. Despite the many advances in systemic therapy and liver-directed treatments, approximately 86% of patients with advanced disease die within 5 years of the diagnosis [3]. The current statistics pose a challenging target for both clinicians and researchers and underscore the need for novel therapeutic approaches in treating metastatic colorectal cancer (mCRC). This review highlights the current role of immunotherapy and their specific adverse effects in patients with mCRC with a special focus on immune checkpoint inhibitors.

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Literature selection

We researched sources published in the English language between January 2000 and August 2018 and listed within the PubMed database (http://www.pubmed.com) using combinations of the key phrase "metastatic colorectal cancer" with one of the following: "immunotherapy," "checkpoint inhibitors," and "cancer vaccine." We also reviewed the

proceedings of international cancer conferences and current guidelines made by major cancer societies, including the European Society of Medical Oncology (ESMO), the American Society of Clinical Oncology (ASCO), and the Society for Immunotherapy of Cancer (SITC). The number of articles was expanded by the inclusion of relevant studies after prior manual analysis of any review articles. The information on ongoing clinical studies was obtained from the online database of the National Institute of Health (https://clinicaltrials.gov/ct2/home).

Systemic therapy—the predecessor of immunotherapy

Currently, most patients with mCRC are treated with a combination of a cytotoxic and a biologic agent. There are several factors influencing the treatment choice in patients with mCRC. For example, patient characteristics including age; performance status; comorbid illness; prior systemic therapy; tumor characteristics including resectability, location, and disease burden; molecular characteristics including rat sarcoma homolog family (RAS), B-raf proto-oncogene, serine/threonine kinase (BRAF), microsatellite instability (MSI), and human epidermal growth factor receptor 2 (HER2) status; and patient preference [4]. In general, combination chemotherapy with or without a biologic agent is associated with higher response rates, a better progression-free, and overall, survival compared with monotherapy. Several randomized-controlled trials have confirmed the efficacy of various regimens in mCRC that are comprised of combinations of oxaliplatin or irinotecan plus fluorouracil (5-FU) or capecitabine (e.g., FOLFOX, CAPOX, FOLFIRI, CAPIRI, and FOLFIRINOX) with the option of adding a vascular endothelial growth factor (VEGF) inhibitor or epidermal growth factor receptor (EGFR) inhibitors [5–13]. In case of cancer progression on one regimen, an alternate regimen containing a different cytotoxic backbone is recommended, for example an irinotecan-based regimen following progression on an oxaliplatin-based regimen. In chemotherapy refractory disease, the disease can be addressed with regorafenib, a multi-tyrosine kinase inhibitor, or trifluridine, an antiviral drug, with tipiracil [14, 15]. However, the benefit of these agents remains modest [16].

The rationale behind the use of immunotherapy in mCRC

Evidence suggests that although the immune system is able to generate an immune response to malignant colorectal cells, due to the complex tumor microenvironment and the immunosuppressive effect of inhibitory cytokines and blood cells, the immune response is not sufficient to prevent tumor growth [17]. The classic model of CRC development is the adenoma-carcinoma sequence, supported by epidemiological evidence and pathology findings [18–22]. Based on this scheme, it is plausible that malignant cells are able to accumulate a number of immunogenic mutations, such as microsatellite instability, and become a potential target for immunotherapy, even though they remain less immunogenic than melanoma or the non-small cell lung cancer [23]. In addition, the neoplasm's progression to metastatic disease is supported by the epithelial-mesenchymal transition (EMT) [24]. According to this theory, mCRC with upregulated pathways for EMT is associated with a higher potential for metastasis development. Knösel and colleagues have demonstrated differential genetic properties of metastatic lesions including aberrations in chromosomal structures compared to the primary focus [25, 26]. In light of rising tumor genetic abnormalities, immunotherapy can be an effective therapeutic intervention in patients with mCRC.

Approaches and mechanisms in immunotherapy

Immunotherapy focuses on selectively enhancing the host's immune response against the malignant disease. Over recent years, there has been a rapid development in this field. The various types of immunotherapy include checkpoint inhibitors that suppress the immune system's inhibition by malignant disease, cancer vaccines including passive immunization with autologous cells or vaccines with gene vectors, oncolytic virus therapy, and T cell bispecific antibody targeting carcinoembryonic antigen (CEA) on tumor cells and cluster of differentiation 3 (CD3) on T cells (Table 1) [27, 28]. It is important to note that the researchers, James P. Allison and Tasuku Honjo, shared the 2018 Nobel Prize in Physiology or Medicine for their pioneering work in the development and understanding of the mechanisms of checkpoint inhibitors.

Checkpoint inhibitors

The first substance identified from the group of immune checkpoint blockers (ICB), ipilimumab, has been used since 2011 after showing a positive association with survival in patients with metastatic melanoma [29, 30]. The rationale behind developing this substance and others in this family relies on the fact that cytotoxic T lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), and PD-2 are responsible for inhibiting the immune processes mediated by T cells [31, 32]. They regulate T cell functions in response to cancer, acute and chronic infection, and autoimmunity (Fig. 1).

CTLA-4 (CD152) is a surface antigen, which was observed to be present on the surface of activated CD8-positive T cells. CTLA-4 opposes the costimulating T cell receptor (CD28)

Table 1 Overview of current and potential immune therapeutic approaches in metastatic colorectal cancer

Type	Agents	Mechanism of action
Checkpoint inhibitors	Ipilimumab	CTLA-4 blockage
	Tremelimumab	CTLA-4 blockage
	Nivolumab	PD-1 blockage
	Pembrolizumab	PD-1 blockage
	Atezolizumab	PDL-1 blockage
	Avelumab	PDL-1 blockage
	Durvalumab	PDL-1 blockage
Cancer vaccines	Autologous, peptide, viral vector, and dendritic cell	Elicit an anti-tumor immune response
Adoptive cell transfer	Chimeric antigen receptor T cell therapy	Directly kill cancer cells
Oncolytic virus therapy	Oncolytic herpes simplex virus, NV1020	Genetically engineered or naturally occurring virus that selectively replicates in and destroys cancer cells without harming normal tissue
IDO1-inhibitors and anti-OX40 agonist	Epacadostat	Enhance immune response
	Indoximod	
	MEDI6469	
Carcinoembryonic antigen T cell biphasic antibody	RO6958688	T cell bispecific antibody targeting CEA on tumor cells and CD3 on T cells

since it is homologous to CD28 and competes for the same binding proteins [33]. In addition, Haanen and Robert observed that mice with CTLA-4-deficiency develop severe, fatal autoimmune diseases [34]. CTLA-4's structure interacts with the CD80 and CD86 proteins contributing to phosphatase activation, resulting in overall deactivation of T cells [31, 35, 36]. Ipilimumab was the first of the CTLA-4 inhibitors to be studied to show benefit in malignant melanoma. There are several ongoing studies evaluating use of the CTLA-4 inhibitors, ipilimumab and tremelimumab in mCRC (see below).

PD-1 and programmed cell death ligand-1 (PD-L1) blockers represent another ICB group, consisting of five antibodies currently approved for treatment. Nivolumab and pembrolizumab target PD-1 structures on CD8-positive T cells, whereas atezolizumab, avelumab, and durvalumab target PD-L1 on the tumor itself (Table 1) [37]. The rationale behind usage of these substances is similar to that for CTLA-4 inhibitors; disinhibition of the immune system's T cells [31]. Experimental research on PD-1 or PD-L1 inhibitors has shown that blocking PD-1/PD-L1 restores anticancer immunity and promotes T cell-mediated cancer cell killing [38]. Finally, the emergence of PD-1 inhibitors created new scientific research initiatives, e.g., determining if receptor inhibition can be achieved by using simpler molecules than antibodies. A research group using an x-ray technique from the Cracow University demonstrated that four non-antibody substances based on (2-methyl-3-biphenylyl) methanol act similar to checkpoint inhibitors by binding to cells and covering the PD-1 binding domain of the PDL-1. These simple molecules could be easier to produce compared to the protein-based checkpoint inhibitors and prove to be less costly [39]. New, more potent and less toxic antibodies are also under investigation [40].

Recently reported findings on checkpoint inhibitors

To date, the benefit of immunotherapy is mostly confined to a small subset of patients with deficient mismatch repair (dMMR) CRC that only represents about 4–5% of patients with mCRC (see the section on "Predictive biomarkers"). Pembrolizumab and nivolumab are two PD-1 inhibitors that have been evaluated alone or in combination with a CTLA-4 inhibitor in patients with chemorefractory mCRC. In the phase I trial, KEYNOTE 016, patients with both dMMR and proficient mismatch repair (pMMR) chemorefractory mCRC and 11 other solid tumors were treated with only the PD-1 inhibitor pembrolizumab [41]. In a subgroup of patients with dMMR tumors, an objective radiographic response rate of 53% with a 21% complete response rate was observed [42]. Patients with dMMR mCRC had a response rate of 40% (4 of 10) compared with a 0% (0 of 18) response rate in patients with pMMR mCRC. The updated results in 40 patients with dMMR mCRC reported a response rate of 52% with an estimated 2-year progression-free survival rate of 53%. Fatigue, pruritis, nausea, diarrhea, anorexia, skin rash, fever, cough, shortness of breathing, musculoskeletal pain, and constipation are common side effect to pembrolizumab. In the KEYNOTE 016 study, adverse effects were as followed: rash and pruritus (25%), diarrhea/colitis (11%), arthralgia (15%), thyroid dysfunction (11%), and fatigue (9%). Grade 3-4 or severe toxicities were noted in 14% including pancreatitis (4%) and diarrhea, colitis, thrombocytopenia, leukopenia, and anemia in 2% each.

In the open label phase 2 study, CheckMate-142, a cohort of 74 patients was treated with the PD-1 inhibitor, nivolumab, and a similar positive effect in patients with dMMR chemorefractory mCRC was observed [43]. Overall, 31% of patients had an objective response and 69% had disease control for 2 weeks or longer. Response to immunotherapy was observed irrespective of tumor PD-L1 expression (29% responded in the PD-L1 positive group, 28% in the PD-L1 negative). Further, the response was independent from the BRAF (25% response rate) or Kirsten ras (KRAS; 27% response rate) mutation status and history of Lynch syndrome (33% with vs. 29% without positive history). Median duration of response was not reached at the time the study was reported. All patients who responded to treatment were alive, and eight had responses lasting 12 months or longer (Kaplan-Meier 12-month estimate 86%, 95% CI 62–95). Overall, the study showed that nivolumab is an effective monotherapy in dMMR colorectal cancer. All-cause adverse events

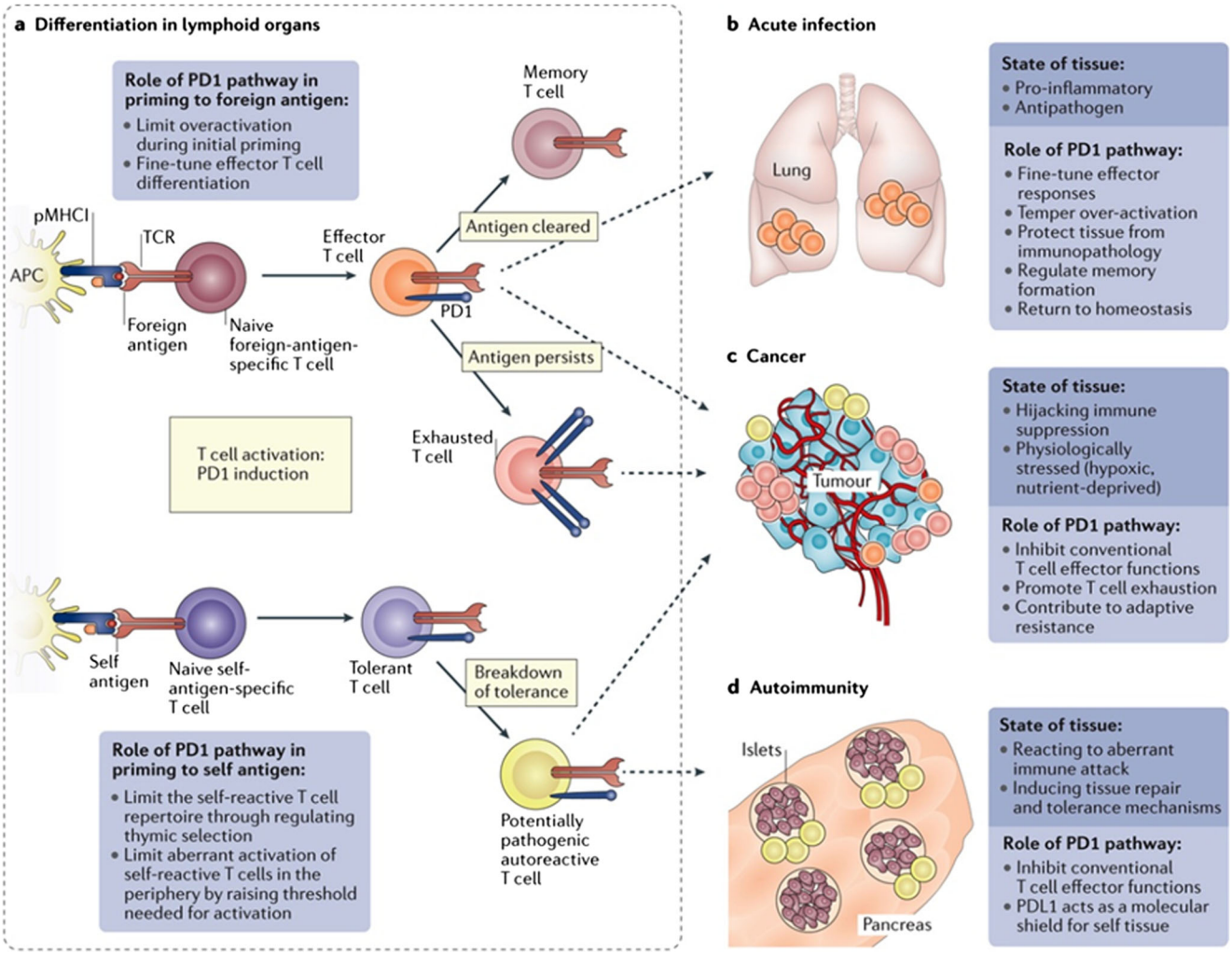

Fig. 1 Roles of PD1 in cancer, acute infection, and immune tolerance. **a** Programmed cell death protein 1 (PD1)-mediated immune regulation in secondary lymphoid organs. PD1 becomes expressed by all T cells during activation. Following exposure to foreign antigens (top), if antigen is cleared, memory T cells form and PD1 expression levels decrease. If antigen persists, T cell exhaustion can develop and PD1 expression levels remain high. PD1 also can be expressed following self antigen encounter (bottom) and can prevent the activation of autoreactive cells. **b–d** The roles of PD1 in non-lymphoid tissues. **b** During acute infection (for example, in the lung), PD1 plays roles in fine-tuning effector T cell responses, tempering overactivation, limiting immunopathology, and regulating memory T cell formation and the return to tissue homeostasis. Here, the tissue is in a pro-inflammatory state; expression of PD1 ligands is a normal response to inflammation. **c** During cancer progression, PD1 can inhibit T cell effector functions and promote T cell dysfunction. Here, elevated physiological stress (for example, hypoxia, and nutrient deprivation), a number of immune suppression mechanisms, including expression of PD1 ligands, and the prevalence of dysfunctional T cell subsets (either exhausted or tolerant) serve as obstacles for protective immunity. Infiltrating T cells can also further induce programmed cell death 1 ligand 1 (PDL1) expression through pro-inflammatory cytokine production, contributing to adaptive resistance. **d** During the development of autoimmunity, the breakdown of peripheral tolerance allows infiltration of pathogenic autoreactive T cells from the draining lymph node to the target organ (for example, the pancreatic islets). Here, PDL1 in the target tissue can act as a molecular shield to limit T cell attacks. The tissue reacts to aberrant immune attack, inducing tissue repair and tolerance mechanisms for protection. Solid lines indicate T cell differentiation; dashed lines indicate trafficking of T cells to different non-lymphoid tissues. APC, antigen-presenting cell; pMHCI, peptide–MHC class I complex; TCR, T cell receptor (reproduce with permission Arlene H. Sharpe, Kristen E. Pauken. The diverse functions of the PD1 inhibitory pathway. Nature Reviews Immunology. Springer Nov 13, 2017)

were reported in 73 (99%) of 74 patients: 29 (39%) had grade 1 or 2 events, 30 (41%) had grade 3 events, 10 (14%) had grade 4 events, and 4 (5%) died due to adverse events that were not related to treatment. Grade 1 and 2 adverse effects were as followed: fatigue (22%), diarrhea (20%), pruritus (14%), rash (11%), hypothyroidism (10%), hepatitis (7%), arthralgia (4%), fever (4%), pancreatitis (4%), and stomatitis (2%). Grade 3 and 4 adverse effects were as followed: pancreatitis (8%), and fatigue, diarrhea, colitis, hepatitis and adrenal insufficiency in 1% each.

Trials are ongoing to assess the efficacy of the PD-L1 inhibitors, atezolizumab, avelumab, and durvalumab in patients with mCRC. Despite promising results in an early phase trial, atezolizumab with and without the mitogen

Table 2 Overview on checkpoint inhibitors with ongoing studies comparing the IBC to established therapies in mCRC (AE, adverse effects; ORR, objective response rate; MTD, maximum tolerated dose; PFS, progression-free survival; TKI, tyrosine kinase inhibitors)

Substance	NCT number	Intervention with main therapy components	Key objectives and outcomes
Ipilimumab			
CTLA-4 blocker	NCT02060188	Refractory carcinomas along mCRC (Nivolumab ± Ipilimumab)	Response rate in MSI-high and non-MSI-high patients
	NCT03350126	Ipilimumab + Nivolumab controlled by Nivolumab alone	Disease control in mCRC
	NCT03271047	Bimetinibe + Nivolumab ± Ipilimumab in MSS mCRC with RAS mutation	Phase 1b study (MTD)
	NCT03377361	Trametinib + Nivolumab ± Ipilimumab in mCRC	AE and objective response rate
	NCT03507699	Nivolumab + Ipilimumab + radiosurgery in mCRC with liver metastases	Response rate and progression-free survival
	NCT03442569	Panitumumab + Nivolumab + Ipilimumab	Overall response rate, progression-free survival
Tremelimumab			
CTLA-4 blocker	NCT03007407	Durvalumab + Tremelimumab in mCRC progressing under chemotherapy	ORR, clinical benefit, AE frequency
	NCT03122509	Durvalumab + Tremelimumab along radiation	Overall response rate
	NCT03202758	Durvalumab + Tremelimumab + FOLFOX in mCRC	Evaluation of the combination's safety
	NCT03005002	Durvalumab + Tremelimumab in MSS mCRC with liver metastases	AE Incidence, response of the metastatic site
	NCT0288743	Durvalumab + Tremelimumab ± radiation in mCRC or NSCL patients	Overall response rate, PFS, overall survival
Nivolumab			
PD-1 blocker (solely studies focusing only on mCRC)	NCT03547999	Perioperative CV301 vacine + Nivolumab and mFOLFOX6	Overall and recurrence-free survival, response rate
	NCT03307603	Radioembolization + Nivolumab in patients with mCRC	Number of AE, PFS, response rate
	NCT02848443	Trifluridine + Oxaliplatin + Bevacicumab + Nivolumab in mCRC	MTD, dose limiting toxicity, AE number
	NCT03350126	See Ipilimumab	See Ipilimumab
	NCT03576963	Guadecitabine and Nivolumab	MTD, recommended phase 2 dose, AE assessment
	NCT03271047	See Ipilimumab	See Ipilimumab
	NCT03442569	See Ipilimumab	See Ipilimumab
	NCT03507699	See Ipilimumab	See Ipilimumab
	NCT03377361	See Ipilimumab	See Ipilimumab
	NCT03251612	Drug administration based on tumor sensitivity in mCRC	PFS, overall survival
	NCT03169777	Nant CRC vaccine with various immunotherapies in mCRC	AE incidence, ORR
Pembrolizumab			
PD-1 blocker	NCT03182894	Epacadostat + Pembrolizumab + Azacitidine in mCRC	ORR, PFS, recommended phase 2 dose
	NCT02437071	Pembrolizumab + radiotherapy or radioablation in mCRC	Response rate and toxicity
	NCT02260440	Pembrolizumab + Azacytydine in chemorefractory mCRC	ORR, PFS, overall survival
	NCT03626922	Pembrolizumab + Pemetrexed + Oxaliplatin in chemorefractory mCRC	ORR, frequency of adverse effects
	NCT03374254	Pembrolizumab ± Binimetinib ± chemotherapy in mCRC	Dose limiting toxicity, ORR
	NCT02851004	Pembrolizumab + BBI608 (Napabucasin) in mCRC	ORR, PFS, AE
	NCT02981524	Pembrolizumab + Cyclophosphamide + GVAX (vaccine) in mCRC	ORR, AE, PFS
	NCT03274804	Pembrolizumab + Maraviroc in treatment refractory MSS mCRC	Safety and toxicity, disease control
	NCT03168139	Olaptesed ± Pembrolizumab in mCRC and pancreatic cancer	AE, pharmacodynamics, ECG/hematological changes
	NCT03519412	Pembrolizumab and Temozolomide in MMR proficient mCRC	ORR, PFS, overall survival, toxicity
	NCT02837263	Pembrolizumab + stereotactic body radiotherapy in liver-spread mCRC	Recurrence rate after 1 year, disease-free survival

Table 2 (continued)

Substance	NCT number	Intervention with main therapy components	Key objectives and outcomes
	NCT03657641	Pembrolizumab + Regorafenibe in advanced or metastatic CRC	PFS, overall survival, dose limiting toxicity
	NCT02460198	Pembrolizumab monotherapy in advanced or mCRC (Keynote 167)	ORR, disease control rate, duration of response
	NCT02713373	Pembrolizumab + Cetuximab in inoperable mCRC	Incidence of AE, PFS, response rate
	NCT03396926	Pembrolizumab + Capecitabine + Bevacicumab in inoperable or mCRC	Overall response rate and duration, disease control rate
	NCT03251612	See Nivolumab	See Nivolumab
	NCT03631407	Pembrolizumab + Viriviroc in advanced or mCRC	ORR, dose limiting toxicities, AE
Atezolizumab			
PDL-1 blocker	NCT03340558	Atezolizuab + Cobimetinib	Change in lymphocyte infiltration, overall survival
	NCT03555149	Study evaluation (Regorafenib, Atezolizumab, Imprime PGG, Bevacizumab, Isatuximab)	ORR, AEs percentage assessment, PFS
	NCT02291289	Biomarker-based therapy of mCRC with either Cetuximab, FOLFOX, 5-FU, Atezolizumab, Vemurafenib	PFS, overall survival, complete or partial response
	NCT02997228	Chemotherapy + Bevacizumab or Atezolizumab in MSI-H mCRC	PFS, overall survival, ORR
	NCT02788279	Atezolizumab ± Cobimetinib versus Regorafenibe in mCRC	overall survival, PFS, complete or partial response
	NCT03256344	Atezolizumab with Laherparepvec in liver metastasized CRC and breast cancer	AE assessment, toxicity, and laboratory deviations
	NCT02873195	Capeitabine and Bevacicumab ± Atezolizumab in refractory mCRC	PFS, overall survival, ORR, incidence of AE
Avelumab			
PDL-1 block	NCT03150706	Avelumab in MSI-H or POLE mutated mCRC	Changes in CEA, TSH, T3, free T4, EKG, CT, or MRI
	NCT03174405	Avelumab + Cetuximab with FOLFOX in untreated mCRC patients	PFS, patient safety, response rate
	NCT03152565	Avelumab along dendritic cell vaccine in formerly treated mCRC	ICB dosage in combination with dendritic cells
	NCT03186326	Chemotherapy vs. Immunotherapy as 2nd line therapy in MSI mCRC	PFS
	NCT03050814	Standard of care ± Ad-CEA and Avelumab	Patient safety, PFS, immunologic analysis
	NCT03608046	Avelumab + Cetuximab and Irinotecan in treatment resistant MSS mCRC	Response rate and adverse effects
	NCT03169777	NANT vaccine with immunotherapy combination in advanced or metastatic CRC	AE assessment, ORR
Durvalumab			
PDL-1 block	NCT03435107	Durvalumab in MSI-H and POLE mutated mCRC	ORR
	NCT03007407	See Tremelimumab	See Tremelimumab
	NCT03122509	See Tremelimumab	See Tremelimumab
	NCT03202758	See Tremelimumab	See Tremelimumab
	NCT03005002	See Tremelimumab	See Tremelimumab
	NCT03376659	Durvalumab + CV301 with chemotherapy in mCRC and pancreatic cancer	Recommended phase II dose, PFS
	NCT02777710	Pexidartinib and Durvalumab in advanced or metastatic pancreatic and CRC	Dose limiting toxicities, ORR, duration of response
	NCT02888743	See Tremelimumab	See Tremelimumab
	NCT03428126	Durvalumab and Trametinib in MSS mCRC	Max. tolerated dose, best overall response

activated protein kinase kinase 1 (MEK1)/MEK2 inhibitor cobimetinib failed to show benefit over the multi-tyrosine kinase inhibitor, regorafenib, in unselected patients with chemotherapy refractory mCRC [44].

Combination of checkpoint inhibitors as therapy augmentation

One of the current strategies to improve the outcome of CRC being investigated is to combine the newly approved therapies with the current standard of care such as FOLFOX, FOLFIRI, or FOLFIRINOX and biologics in patients with mCRC. This approach could potentially be synergistic as cytotoxic agents damage cancer cells and thereby release antigens that could enhance the immune response against the malignant disease. While waiting for the results from the clinical studies involving combined chemotherapy and immunotherapy, it is important to consider cumulative adverse effects or negative interactions of systemic chemotherapy and immunotherapy. An alternative approach is the combination of two immunotherapeutic agents to enhance the immune response against cancer cells. For example, the combination of nivolumab (PD-1 inhibitor) and ipilimumab (CTLA-4 inhibitor) seems to be a synergistic combination that is yielding better results than the nivolumab monotherapy reported in the CheckMate 142 study [45]. A cohort of 119 patients received a combination of nivolumab and ipilimumab and, after the median follow-up period of 13.4 months, the overall response rate was 55% and disease control rate was 80%. One-year progression-free survival and overall survival rates were 71 and 85%, respectively. Indirect comparisons suggest that although combination therapy is more effective, it results in a greater incidence of major adverse effects. For example, any-grade treatment-related adverse effects were reported in 73% of patients, with the most common being diarrhea (22%), fatigue (18%), pruritus (17%), fever (17%), hypothyroidism (13%), hyperthyroidism (11%), nausea (11%), rash (9%), and hepatitis (7%). Thirty-two percent of patients experienced a grade 3 (27%) or 4 (5%) adverse effects, hepatitis (11%), pancreatitis (4%), anemia (3%), and colitis (3%) occurring in > two patients.

Despite efficacy of checkpoint inhibitors in patients with dMMR mCRC, the economic impact of these therapies is largely remained unknown. Chu and other by using a decision analytic model explored the cost-effectiveness of immune checkpoint inhibitors in mCRC and demonstrated that although both single and dual checkpoint blockade were more effective for dMMR mCRC than chemotherapy, they were not cost-effective, largely because of drug costs [46]. Table 2 presents the ongoing studies on ICBs and their aims and hypotheses.

Pseudo-progression—a possible confounder in effectivity assessment

Pseudo-progression is a phenomenon that must be considered early in treatment with ICB [47]. The frequently observed initial volume increase in imaging studies is likely based upon T cell infiltration. Cytotoxic processes and inflammation initiated at the site contribute to a rise of biochemical markers and a volume increase due to the edema [47]. When it comes to evaluation of immunotherapy effectiveness and disease progression during the early phase of treatment, an independent decision on a case-by-case basis and clinical correlation are important [48].

Tumor vaccination

Tumor vaccines are an active form of immunotherapy that activates a host's immune response against cancer. They have been investigated for both the prevention of recurrent disease and treatment of advanced disease. The typical approach in tumor vaccination includes autologous transplantation of dendritic cells (DCs) which are modified to present tumor antigens and stimulate the acquired immune system. Various types of vaccines have been evaluated in CRC that include autologous, DC, peptide, and viral vectors. To date, tumor vaccines have not shown promising results and we are unaware of any tumor vaccinations being clinically approved for CRC treatment. In the following section, we briefly review various types of vaccines in patients with mCRC.

An autologous vaccine contains tumor-associated antigens (TAAs) from the patient and has been mostly evaluated in a preventive setting, with or without modification by a non-lytic, low pathogenic strain of the Newcastle disease virus [49, 50]. Limited benefit has been shown and therefore they are not used in clinical practice. Peptide vaccines are antigenic epitopes derived from TAAs or tumor-specific antigens (TSAs) [51]. The commonly targeted peptides are CEA, mucin 1, and EGFR, among others. A phase II trial evaluated five human leukocyte antigen (HLA)-A*2402-restricted peptides (three from oncoantigens and two from VEGF receptors) in a single vaccine in 96 patients with chemotherapy-naïve mCRC in combination with oxaliplatin-based chemotherapy and found only limited benefit [52]. DCs are potent TAA-presenting cells in association with major histocompatibility complex (MHC) I and II and trigger T cell immunity. DCs are shown to be safe in patients with advanced malignancies [53]. However, a randomized phase II clinical trial comparing an autologous tumor lysate dendritic cell vaccine to the best supportive care failed to demonstrate disease control or better survival despite a tumor-specific immune response [54]. Viral vector vaccines use a viral vector system to deliver the TAAs and tend to generate a higher immune response than peptide vaccines. A randomized phase II clinical study assessed efficacy of a non-replicating canary pox virus (ALVAC) expressing CEA and B lymphocyte antigen B7 (B7-1; CD80) (ALVACCEA/B7-1) vaccine in 118 patients with mCRC in combination with irinotecan-based chemotherapy using various schedules [28]. No differences were noted in clinical or immune responses between the treatment groups.

Another type of vaccination, that might become relevant for patients with CRC, includes genetic therapy with vector injection containing, e.g., the cytosine deaminase gene, which on translation can generate 5-FU from a non-toxic 5-FU derivate such as 5-fluorocytosine, for which the malignant cells display higher susceptibility [55]. For now, this approach remains experimental. While tumor vaccines are a plausible and promising therapy, the group of checkpoint inhibitors is currently attracting higher attention due to their promising response in various cancers.

Adoptive cell transfer

In this approach, tumor-specific cytotoxic cells are infused into cancer patients with the goal of recognizing, targeting, and destroying tumor cells, and achieving a potent and sustained response [56]. For example, sensitized natural killer (NK) cell transplants depict a newer form of treatment. A benefit has been shown after administration of interleukin 2 (IL-2) or (IL-15) incubated NK cells in refractory mCRC with mutated EGFR status [57]. Further, Cetuximab-resistant tumors, as well as RAS and BRAF mutated neoplasms, have been observed to be susceptible to NK cells obtained from umbilical cords in in vivo mouse models [58, 59]. Similar to the vaccines, tNK cells are still under development and remain a promising, young branch of immunotherapy. Likewise, chimeric antigen receptors (CAR)-T cell immunotherapy increases the immune cells' ability to kill cancer cells by reprogramming them to express CAR protein and selectively binding to the cancer cells. CAR-T cell therapy efficacy has been demonstrated in mouse models of mCRC [60].

Oncolytic virus therapy

Oncolytic viruses are anticancer viruses that selectively infect and damage malignant cells without causing harm to normal tissue. Although they have shown efficacy in other solid tumors such as melanoma, limited evidence is available about their efficacy in mCRC. For example, a phase I/II study assessed the safety and efficacy of a genetically engineered oncolytic herpes simplex virus, NV1020, in patients with previously treated mCRC [61]. Approximately two thirds of patients had disease control with a 1-year survival rate of 47.2%. Currently, no approved oncolytic therapies are available for patients with mCRC.

Indoleamine 2,3-dioxygenase 1 inhibitors and anti-OX40 agonists

Cancer cells and DCs overexpress indoleamine 2,3-dioxygenase 1 (IDO1) in the tumor microenvironment and activation of IDO1 suppresses the immune response against cancer cells [62]. Several clinical trials are evaluating the use of either indoximod or a second generation IDO1 inhibitor such as epacadostat alone, or in combination with other modalities such as immune checkpoint inhibitors in various solid malignancies including pMMR mCRC.

OX40 (CD 134) belongs to the tumor necrosis factor family of receptors and is a T cell costimulatory molecule that affects T cell responses [63]. The active ligand, OX40L, is present on endothelial and other blood cells, including antigen-presenting cells, and augments CD4 and CD8 T cell proliferation, differentiation, and survival. Animal models have supported the efficacy of OX40 agonist tumor growth [64]. Trials are evaluating the combination of OX40 agonist and checkpoint inhibitors in various solid tumors and their role in pMMR mCRC is currently not well defined [65, 66].

CEA T cell bispecific antibody

CEA-T cell bispecific (TCB) is an antibody that simultaneously binds T cells and CEA-positive tumor cells. In a study involving CEA-positive solid tumors, including pMMR chemorefractory mCRC, CEA-TCB antibody was evaluated alone, or in combination with atezolizumab. In the monotherapy arm, 14 (45%) out of 31 patients with mCRC showed either partial response or stable disease [27]. Twenty-five patients were treated with combination therapy, from which nine patients (36%) had either a partial response or stable disease. Late phase trials are in development to assess the efficacy of this compound in pMMR chemorefractory mCRC.

Predictive biomarkers

BRAF and RAS mutation status are known biomarkers in patients with mCRC that determine the prognosis and predictive benefit to anti-EGFR monoclonal antibodies, respectively [67]. The dMMR status is currently the only known biomarker that predicts the response to checkpoint inhibitors. The defect in one or more MMR proteins, MutL homolog 1 (MLH1), MutS homolog 2 (MSH2), MSH6, and postmeiotic segregation increased 2 (PMS2) leads to accumulation of mutations in microsatellite regions which are areas of short tandem DNA repeat that are also known as microsatellite instability-high (MSI-H) [68]. Although about 15% of CRC are dMMR, only about 4% of mCRC are dMMR. As reported above, the use of checkpoint inhibitors as a single agent was not effective in patients with pMMR mCRC. MSI-H or dMMR tumors are usually poorly differentiated and are associated with tumor-infiltrating lymphocytes [69]. Gene expression profile analysis has shown that dMMR tumors have a high frequency of

neoantigen load secondary to the higher rates of mutations compared with pMMR tumors [70].

ICB therapy shows effects mainly in the dMMR setting, with no or limited efficacy in pMMR mCRC, that comprises greater than 90% of the disease. It has been proposed that creation of a T cell infiltrated environment similar to dMMR tumors by combining ICB with other immune-modulating agents could potentially increase the efficacy of ICB in pMMR tumors. For example, Bendell and others evaluated azetolizumab in combination with cobimetinib, a MEK1/2 inhibitor, that may improve tumor immune recognition by increasing MHC I expression, promoting T cell accumulation in tumors, and limiting T cell exhaustion [44]. However, despite promising results in a phase I trial, a confirmatory phase III trial failed to replicate the benefit of combination therapy in pMMR mCRC.

The degree of intestinal lymphocyte infiltration seems to be a predictor of the therapeutic response. An immune score quantification using a measure of CD3-positive and CD8-positive cell densities in the tumor center and invasive margin has been shown to be a robust predictive marker of disease recurrence in patients with early stage colorectal cancer compared with the well-established TNM classification [71–75]. Therefore the efficacy of the recently emerged therapies needs to be evaluated with the immune response measurement, using the immunological scoring system.

Adverse effects with checkpoint inhibitors

In this section, we focus on the ICB-related and specific adverse effects, since this form of treatment is the only immunotherapy currently established in the clinical routine. Upregulation of signal transduction pathways in the immune response explains the specific adverse effects that are linked with ICBs [76]. The toxicity profile of ICB is very different from conventional cytotoxic agents and biologics and could involve any organ system. As mentioned above, rodents without CTLA-4 display severe to fatal, autoimmune conditions. Similar autoimmune responses were observed in various human organ systems, most frequently associated with colitis, hepatitis, or neurological disorders such as myasthenic or myopathic syndromes [77–79]. Nevertheless, the autoimmune effects can also manifest themselves in the structures of the eye, lungs, thyroid, adrenal glands, heart and blood vessels, kidney, skin, and bone marrow [80]. Although in most cases adverse effects are observed within 3–6 months of the commencement of treatment, early or delayed adverse effects are not unusual. It is important to know that side effects involving multiple organ systems can occur synchronously or metachronously and can mimic infections or disease progression. Early recognition of adverse effects and their management are important to avoid serious complications.

Several other reviews and guidelines have described the management of ICBs and the authors would like to refer readers to them for detailed information [81, 82]. In Table 3, we briefly review management of adverse effects involving various organ sites. In general, anti-CTLA-4 agents are more commonly associated with adverse effects whereas anti-PD-L1 inhibitors are less toxic. Most patients develop mild to moderate (grade I and II) adverse effects such as low-grade fever, fatigue, arthralgia, skin rash, impaired liver function test, diarrhea, and dry mouth. Serious adverse effects (grades III and IV) are more commonly observed with anti-CTLA-4 antibodies alone, or in combination with anti-PD-1 or PD-L1 checkpoint inhibitors, and are dose dependent. Most cases of mild to moderate side effects are treated with supportive

Table 3 Overview of the common specific adverse effects related to checkpoint inhibitors

System/organ	Reactions	Likelihood in %	Specific therapy considerations
Gastrointestinal	Flare up of former inflammatory bowel diseases, idiosyncratic liver damage, colitis, ileitis, gastritis, hepatitis, and diarrhea	20–40	Liver and intestinal function monitoring, Infliximab can be considered in steroid refractory diarrhea
Skin	Erythema, exanthema, psoriasiform-, lichenoid-, or pemphigoid lesions	30–50	Immediate therapy discontinuation in Steven Johnson syndrome
Endocrine	Adrenitis, hypophysitis, hyper- and hypothyroidism, hyper- and hypoparathyroidism, autoimmune diabetes	10–50	Early and permanent discontinuation might be necessary
Kidney	Nephritic and nephrotic syndromes	< 2–30	
Nervous system	Myasthenic reactions, Guillain-Barré syndrome, meningitis, encephalitis, and transverse myelitis	< 4–15	Early and permanent discontinuation of ICB for most neurological AEs
Lung	Pneumonitis	1–5	
Hematologic system	Neutropenia and other leukopenia forms, anemia, thrombocytopenia	< 1–5	Colony-stimulating factor
Ophthalmologic	Uveitis, episcleritis, blepharitis	1	
Cardiovascular	Pericarditis, myocarditis, systemic lupus erythematosus	1	

measures with continuation of immunotherapy and a close follow-up. Treatment interruption and high dose steroid therapy is required for the management of severe and serious toxicities. Patients with serious adverse effects usually require hospital admission and supportive measures. Most guidelines recommend usage of 1–2 mg/kg prednisone, or its equivalent, for serious adverse effects. Steroids should be continued for 2 to 4 weeks before tapering off treatment. Most patients respond to a high dose steroid within a week of the initiation of treatment. Patients who fail to respond to a high dose steroid will require other immunosuppressive intervention. Early referral to an appropriate specialist should always be considered. Treatment can be resumed if the adverse effects are not higher than grade I, and prednisone dose is smaller than 10 mg per day [80, 81]. Approximately 50% of patients develop recurrent symptoms or other serious adverse effects and will require permanent discontinuation of treatment. Currently, there is insufficient data on ICB usage by women during pregnancy.

Conclusions

Immunotherapy has the potential to become the new standard of care in the management of mCRC. Even though there are several subgroups of immunotherapies, most of them including cancer vaccines, adoptive cell transfer and CEA-TCB antibodies will require further studies to prove their efficacy in mCRC. Therefore, checkpoint inhibitors are currently the main domain of immunotherapy. Clearly immunotherapy such as checkpoint inhibitors has the benefit of a selective approach in boosting the host's immune response against cancer cells with limited collateral damage. Checkpoint inhibitors offer an alternative with dramatic and durable responses for patients with dMMR mCRC and are approved for patients with chemorefractory dMMR mCRC [83]. Management of pMMR CRC that normally comprises about 95% of all metastatic disease will require novel treatment strategies as they do not respond to single agent checkpoint inhibitors. Monitoring of immune-related adverse effects is required since they are different from cytotoxic treatment-related toxicities and can affect any organ system. These side effects are treated with high dose steroids and supportive measures. Further studies are ongoing to better understand the potential resistance of pMMR tumors. New strategies include combining checkpoint inhibitors with chemotherapy, VEGF inhibitors, vaccine, and CEA-TCB antibodies. In conclusion, immunotherapy stays a new and promising alternative. With gradual progression of the research and findings, it may soon become an alternative to the classical systemic therapy.

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