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Review Article

Immunotherapy in Colorectal Cancer: A Promising Avenue?

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Abstract

Advancements in immunotherapy, particularly immune checkpoint inhibitors, have revolutionized the treatment of metastatic colorectal cancer (mCRC). However, the efficacy of available immunotherapeutic agents is largely limited to tumors with DNA mismatch repair-deficient (dMMR) and/or those with microsatellite instability-high (MSI-H) mCRC. Hence, only a small subset of patients with mCRC can potentially benefit from currently available immunotherapeutic drugs. In this review article, the role and future perspectives of novel immunotherapeutic agents in the management of patients with colorectal cancer will be outlined.

Introduction

Patients with metastatic colorectal cancer (mCRC) have traditionally been treated with systemic chemotherapy. More recently, the introduction of novel targeted and immunotherapeutic drugs has revolutionized the management of patients with metastatic malignancies. Since its advent in 1893 by Dr. William Coley, the father of cancer immunotherapy, there have been exemplary advancements in the field of immunotherapy, extending its application to a wide variety of cancers [1]. Major randomized trial reported improved prognosis and oncologic outcomes with the use of immunotherapy in patients with mCRC [2].

However, its efficacy is largely limited to tumors with abundant expression of checkpoint receptors (i.e. programmed death; P.D.1, programmed death ligand 1; PD-L1 and cytotoxic T-lymphocyte associated antigen; CTLA-4), particularly those with mismatch repair-deficient (dMMR) and/or high levels of microsatellite-instability (MSI-H) [3-5].

This review discusses the current role of immunotherapeutic agents and the potential for future novel immunotherapeutic agents in the management of mCRC.

Mechanisms of Action of Currently Available Immunotherapeutic Drugs

PD-1 Inhibitors (Pembrolizumab and Nivolumab):

Programmed cell death protein 1 (PD-1) is located on T-cells, and programmed death-ligand 1 (PD-L1) is mainly found on mutated tumor cells and abnormal immune cells. When PD-1 and PD-L1 interact, T-cell dysfunction and exhaustion occur, thus preventing the immune system from mounting an anti-tumor T-cell response. By blocking PD-1 on T-cells, PD-1 inhibitors, such as Pembrolizumab and Nivolumab, prevent this interaction and augment the anti-tumor T-cell response [6-8].

CTLA-4 Inhibitors (Ipilimumab):

In a normal anti-tumor immune response, T-cells are activated by antigen-presenting cells (APCs). Proliferation of the T-cell is then signaled via co-stimulation of B7 on the APC with CD28 on the T-cell. CTLA-4, when present on a T-cell, acts as a decoy by binding to the APC-B7 protein, thus preventing B7 interaction with CD28. This stops co-stimulation from occurring, disabling T-cell survival and proliferation and preventing adequate immune response. CTLA-4 inhibitors prevent the interaction of CTLA-4 with B7. This allows prolonged survival of T Cells and a longer lasting activity against tumor cells [9].

PDL-1 Inhibitors (Atezolizumab, Avelumab, and Durvalumab):

These agents block PDL-1 on the mutated tumor cells, thus have a similar mechanism of action to the PD-1 inhibitors as discussed earlier [10].

Role of Immunotherapy in the Management of Colorectal Cancer

Several landmark clinical trials have evaluated the role of novel immunotherapeutic agents in the management of mCRC with promising results, subsequently gaining FDA approval (Table-1) [11-13]. A series of KEYNOTE trials investigated the efficacy of Pembrolizumab among patients suffering from mCRC with dMMR/MSI-H mutation. In the KEYNOTE-164 trial, 124 patients were divided into 2 cohorts based on the status of prior treatment, cohort A (≥2 lines of systemic therapy) and cohort B (≥1 line of systemic therapy). The treatment protocol comprised administration of intravenous Pembrolizumab every 3 weeks for a maximum of 35 cycles. The duration of treatment was reduced for patients experiencing adverse effects and/or disease progression. The study reported an Objective Response Rate (ORR; the proportion of patients with complete response or partial response) of 33% in both cohorts [3]. The ongoing KEYNOTE-177 trial

will compare oncologic outcomes in patients receiving Pembrolizumab compared to those receiving the standard chemotherapy regimen in patients with MSI-H/dMMR mCRC [14].

Table 1: *FDA approved immunotherapies for the treatment of mCRC*

Immunotherapy	Mechanism of action	Approval year	Associated landmark trial
Pembrolizumab*	PD-1 inhibition	2017	KEYNOTE Trials
Nivolumab**	PD-1 inhibition	2017	CheckMate-142
Nivolumab + Ipilimumab**	PD-1 inhibition + CTLA-4 inhibition	2018	CheckMate-142

*Therapy is approved for adult and pediatric patients with unresectable or mCRC with MSI-H or dMMR who have no satisfactory alternative treatment options or with MSI-H who have progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan [11].
**Therapies are approved for patients greater than 12 years old for mCRC with MSI-H or dMMR solid tumors that have progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan [12,13].

In the CHECKMATE-142 trial, response to treatment with Nivolumab in patients with dMMR/MSI-H mCRC was evaluated. The study included patients with biopsy proven mCRC who failed first line chemotherapy, including Fluoropyrimidine and Oxaliplatin or Irinotecan. The treatment protocol included patients receiving Nivolumab every 2 weeks. The treatment duration was reduced if patients developed adverse effects, had progression of disease or death. Out of the 74 participants, ORR was calculated to be 31.1% [15]. The drug was subsequently approved by the FDA for patients who failed first line of chemotherapy for mCRC [16]. The combination therapy of Nivolumab and Ipilimumab was also substantiated from this trial with an ORR of 54.6% among this cohort [15]. However, this combination is rarely used since monotherapy with PD-1 inhibitors is highly effective in most patients [13,17].

MSI status is a strong predictor of the efficacy of checkpoint inhibitors in mCRC [18]. dMMR/MSI-H metastatic tumors are more responsive to immunotherapy when compared to mismatch repair deficient-microsatellite stable (pMMR/MSS) tumors [15]. Most CRCs are pMMR/MSS, hence, there is a small proportion of patients with mCRC who may potentially benefit from the currently FDA-approved immunotherapies [19].

Safety and Adverse Drug Events (ADE) Related to Immunotherapeutic Drugs

As immunotherapy has become a standard treatment for patients with advanced or mCRC, adverse drug events (ADEs) have been characterized in detail, especially immune-related adverse events (irAEs), which occur commonly from use of checkpoint inhibitors [20]. The mechanism behind irAEs is not completely understood but is thought to be due to immune system dysregulation [21].

In KEYNOTE-164, patients using Pembrolizumab were found to have ADEs in 62% (n=38) of patients in cohort A and 70% (n=44) in cohort B [3]. Adverse events reported in cohort A included arthralgias (16%, n=10), nausea (16%, n=10), diarrhea (13%, n=8), asthenia (13%, n=8), pruritus 13% (n=8), and fatigue (10%, n=6) [3]. The most frequent ADEs in cohort B included hyperthyroidism (17%, n=11), fatigue (17%, n=11), arthralgias (11%, n=7) and diarrhea (11%, n=7) [3].

A recent retrospective analysis of 1498 patients from 14 clinical trials revealed that skin and gastrointestinal (GI) tract side effects were the most common among patients receiving Ipilimumab, with 44.9% of patients experiencing a dermatologic and 32.5% experiencing a GI ADEs [22]. The most commonly reported GI ADE was diarrhea (27-31%), while the most common dermatological ADE was pruritis (24.4%) [23].

Nivolumab, according to a recent metanalysis, has a higher safety profile compared to Pembrolizumab and Ipilimumab [24]. In the CheckMate-142 trial, ADEs were assessed in patients with dMMR/MSI-H, the most common low-grade complications were fatigue (22%, n=16), diarrhea (20%, n=15), pruritus (14%, n=10), and rash (11%, n=8) [15]. A 2018 meta-analysis included 6173 patients who had received Nivolumab, reported a serious complications rate of 11.2% (n=196) and drug related mortality rate of 0.3% (n=13) [25]. Among patients using combination therapy of Nivolumab and Ipilimumab, the most common ADEs included diarrhea (22%, n=26), fatigue (18%, n=21), pruritus (17%, n=20), and pyrexia (15%, n=18) [15].

The majority of the previously mentioned immunotherapy related ADEs can be effectively managed with close monitoring, supportive therapy, temporary discontinuation of immunotherapy, and/or mild immunosuppressive agents, such as corticosteroids [21].

Resistance

The initial favorable response to immunotherapeutic agents may, later, be dampened due to development of resistance by the target cells [26]. Thus, the use of multi-agent immunotherapy may provide an added benefit in such patients [26]. Tumor resistance to immunotherapy may be primary, indicating initial resistance to therapy or acquired throughout treatment [26]. The varying modes of resistance have not been entirely classified and provide an avenue for future investigation [6,18,27].

Future Directions for Therapy

The ATOMIC trial is an ongoing, phase-III, study investigating the potential benefit of using a combination of FOLFOX (Oxaliplatin, 5- Fluorouracil and Folinic acid) with Atezolizumab as an adjuvant treatment of stage-III CRC [27]. The ongoing AVETUX trial is a phase-II trial that is exploring the efficacy of FOLFOX and Cetuximab as the first line regimen among patients with RAS/ BRAF mutation (MSI or MSS subtype) in terms of progression free survival (PFS) at 12 months [28]. The NCT03373188 randomized phase-I trial is studying the efficacy of anti-semaphorin 4D (anti-SEMA4D) monoclonal antibody VX15/2503 with or without Ipilimumab or Nivolumab in patients with stage-IV CRC with hepatic metastasis and can be removed by surgery [29]. The phase-II, NCT03435107 trial is currently investigating the role of durvalumab monotherapy as a second line therapy in mCRC patients with dMMR/MSI-H or POLE mutation [30]. The phase-II, NCT03435107 trial is currently investigating the role of durvalumab monotherapy as a second line therapy in mCRC patients with dMMR/MSI-H or POLE mutation [31].

Several other studies are currently investigating novel experimental drugs against other potential immunologic targets, such as, IL-6 [31], IL-21 [32], and TGF-β [15]. These include the EORTC ILOC trial that is exploring the role of Durvalumab with Tremelimumab combined with local ablation in mCRC with non-respectable hepatic metastasis [33,34].

Conclusion

Immunotherapy is a promising treatment in patients with mCRC, particularly those with dMMR/MSI-H mutation. Several ongoing trials are exploring the potential role of novel immunotherapeutic agents, either alone or in combination with systemic chemotherapy for patients who do not possess those mutations.

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