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Review Article

Immunotherapy in Colorectal Cancer: A Review

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ABSTRACT

In the world, colorectal cancer is the second most deadly and third most frequent type of cancer. Dietary and behavioural style are the primary predisposing cause. Traditional therapies like surgery, radiation, and chemotherapy are the mainstay of treatment for this disease. More efficient therapies with fewer adverse effects are desperately needed because of its high prevalence and high morbidity. Immunotherapy is one of the fastest-growing treatments and has emerged as a possible therapeutic alternative in recent years. By boosting the immune system's ability to identify and combat cancer cells, immunotherapy prevents the growth of tumors. The most recent immunotherapies for oncolytic viruses, tumor-infiltrating lymphocytes, cell therapy, and immune checkpoint inhibitors are discussed in this study. Some of these are utilized in therapeutic treatment and have demonstrated encouraging outcomes in clinical trials.

KEYWORDS

Colorectal Cancer, Immunotherapy, Immune Checkpoint Inhibitors, Adoptive Cell Therapy, Oncolytic Virus

INTRODUCTION

With around 1.9 million cases, colorectal cancer (CRC) is the second most relevant cause of cancer-related deaths worldwide and the third most common cancer overall [1]. As such, it is one of the most important public health issues. A satisfactory therapeutic outcome can be obtained with early diagnosis and treatment. However, if the diagnosis is made in the late stages of metastatic disease, the survival rate is only 13.1%. Changes in human lifestyle, such as a decrease in physical activity and an increase in the consumption of high-fat foods, are contributing to the rising prevalence of colorectal cancer [2]. By 2030, there will likely be 1.1 million CRC-related deaths and over 2.2 million new cases globally, presenting a major hazard to human health.

With various molecular pathways implicated in tumor growth and metastatization, colorectal cancer is a genetically a set of different disease [3]. Normal epithelial cells often give way to unchecked proliferative epithelial cells that evolve into polyps and carcinoma, respectively, throughout the course of colorectal cancer development [4]. According to histology, the most prevalent type of colorectal cancer is adenocarcinoma. Surgical procedures, chemotherapy, and radiotherapy are examples of traditional therapeutic modalities [5]. Depending on the tumor's location and mechanism of invasion, the clinician typically uses a range of combination therapy to increase patient survival. Surgery may be the best alternative of action for confined cancers. Cancer cells are not eliminated, though, and tumor recurrence is typically caused by cancer cells that remain in the local tissue, blood, and lymphatics. Immunotherapy, which has expanded quickly in recent years, uses postoperative adjuvant chemotherapy, innate and adaptive immunity, and immunotherapy to detect and eliminate any remaining cancer cells with good therapeutic results [6].

Microsatellite instability (MSI), CPG island methylation, and chromosomal instability are the three primary forms of genetic instabilities in colorectal cancer (CRC) [7]. A family of small tandem repeat DNA sequences made up of 1–6 nucleotides that are equally dispersed throughout the genome, rich in polymorphism information, and simple to identify is referred to as microsatellite [8]. Microsatellites, commonly referred to as microsatellite stability (MSS), are typically rather conservative. However, double-stranded DNA replication factors can cause repeats to be inserted or deleted in disease states like malignancies, and replication mistakes can result in the formation of novel microsatellite alleles [9]. One of the most thoroughly researched molecular markers in colorectal cancer is MSI. Microsatellite stabilization (MSS) is linked to chromosomal instability (CIN), whereas mismatch repair (MMR) gene inactivation is indicated by MSI and typically accompanied by a CpG island methylation phenotype. MSI was present in about 15% of CRC patients, whereas MSS was prevalent in the remaining patients. Although they haven't been thoroughly investigated, MSI CRC has more point mutations than MSS CRC. Short nucleotide repeats, tiny insertions, and deletions (insertion deletions) account for the majority of mutations. Genes that boost cell growth by causing loss-of-function mutations in microsatellites or MSI target genes have been thoroughly investigated; several of these genes have been identified as potential targets and are therefore regarded as tumor suppressors. A common indicator for the diagnosis, management, and prognosis of genetic disorders and various malignancies is the heterogeneity of microsatellite status.

To prevent tumor progression, immunotherapy is a therapeutic strategy that strengthens and stimulates the immune system to identify and destroy cancer cells [10]. To defend the body and eliminate infections, foreign cells the immune system is made up of a range of cells, tissues, and organs located throughout the body [11]. Tumor-infiltrating lymphocytes (TILs), chimeric antigen receptor (CAR)-T cells, immune checkpoint inhibitors (ICIs), and oncolytic virus treatment (OVT) are examples of immunotherapy [12,13]. According to studies, immunotherapy works effectively for melanoma, bladder cancer, lung cancer, and several forms of blood cancer. Four immunotherapy techniques for the treatment of colorectal cancer are presented in this review along with an explanation of their mechanics and a discussion of the prospects and difficulties facing immunotherapy research.

The goal is to help CRC patients comprehend immunotherapy techniques, access the possibility of recovery, and broaden the researchers' research ideas.

IMMUNOTHERAPY

Inhibitors Of Immune Checkpoints

T cell-expressed molecules known as immunological checkpoints, block T cells during the immune response and stop the autoimmune reaction [14]. Immune checkpoint inhibitors (ICIs) activate T cells, release killer factors, and kill tumor cells by binding to receptors and interfering with immunosuppressive communication between antigen-presenting cells (APCs), tumor cells, and T cells [15]. Due to the significant degree of genetic and molecular heterogeneity in CRC, treatment must be tailored to each patient's [16]. The human genome contains highly polymorphic repeating DNA sequences called microsatellites. CRC was divided into two molecular pathological groups by the Cancer Genome Atlas (TCGA) project using thorough molecular analysis (chip-based sequencing technique). Microsatellite instability (MSI) and microsatellite stability (MSS) CRC are two examples of these [17]. The absence of MMR causes the cancer cells in about 13% of tumors to become genomically unstable. According to the frequency of microsatellite marker instability, MSI CRC, which makes about 15% of all sporadic CRC, is classified as either MSI-low (MSI-L) or MSI-high (MSI-H) [18]. Selective monoclonal antibodies against cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), programmed cell death ligand-1 (PD-L1), and programmed cell death-1 (PD-1) are among the ICIs that MSI-H usually responds to over time (Table 1) [19]. On the other hand, over 85% of CRC patients with microsatellite stable (MSS) tumors usually do not respond to ICI. CTLA-4 and PD-1 are currently the most well-known immune checkpoints of CRC treatment [20,21].

The first immune checkpoint identified by James Allison in the 1990s, CTLA-4, is another important target. Research revealed that CTLA-4 and CD28 can bind to costimulator B7 in a competitive manner, and that the immunosuppressive impact upon binding was noticeably greater than that of CD28 by itself [22]. The first CTLA-4 mab, ipilimumab, also known as Yervoy, was authorized in 2011 for the treatment of melanoma. It was a whole human monoclonal antibody against CTLA-4 [23]. Later, scientists discovered that ipilimumab had a positive therapeutic impact on metastatic colorectal cancer (mCRC) [24]. Nevertheless, during clinical use, it was discovered that ipilimumab caused serious immune-mediated side effects in CRC patients, including as rash, musculoskeletal pain, diarrhea, and fatigue. Ipilimumab therapeutic impact draws a lot of researchers who are attempting to minimize adverse effects by mixing other drugs. Nivolumab plus low-dose ipilimumab as a first-line treatment for patients with high/mismatch repair deficiency (MSI-H/dMMR) (mCRC) showed strong and long-lasting clinical benefit with good tolerability, according to a phase 2 clinical trial involving 141 participants [25]. The efficacy of this combination therapy approach was further supported by the study's 4-year follow-up data [26].

The most crucial receptor for triggering T-cell expression and inducing immunosuppression is programmed cell death protein 1 (PD-1), whereas programmed cell death ligand 1 (CD274, PD-L1) contributes to programmed death, which results in T cell apoptosis or inactivation [27]. In MSI-H or dMMR CRC, PD-1 blockade was linked

to a considerably longer progression-free survival and fewer treatment-related adverse events than chemotherapy, according to a phase III trial [28]. Evidence of PD-1 pathway-mediated tumor immunity was first documented in 2002. Tumor cells employed T-cell receptor recognition to further suppress immunity and elude immune surveillance after PD-1 binds to PD-L1, which in turn greatly increased tumorigenesis and invasion [29]. Inhibitors of PD-1/PD-L1 can further increase T-cell activation by preventing T-cell malfunction and death. Only a small percentage of CRC patients with high levels of microsatellite instability and deficient mismatch repair (dMMR/MSI-H) responded to anti-PD-1/PD-L1 therapy. Nivolumab and pembrolizumab, two monoclonal antibodies that demonstrate good and durable therapeutic results, were approved by the FDA in 2014 for the treatment of dMMR/MSI-H colorectal cancer [12]. In the first-line treatment of dMMR/MSI-H mCRC, the KEYNOTE-177 study compared the effectiveness of pembrolizumab versus standard chemotherapy. The median progression-free survival (PFS) with pembrolizumab was 16.5 months (95% CI 5.4–38.1), while the median PFS with chemotherapy was 8.2 months (6.1–10.2) (HR 0.59, 95% CI 0.45–0.79) [30]. 95 out of 143 patients (66%) receiving chemotherapy and 33 out of 153 patients (22%) receiving pembrolizumab experienced treatment-related adverse events of grade 3 or worse. In patients with MSI-H/dMMR mCRC, pembrolizumab monotherapy was linked to longer PFS, higher objective and complete responses, and fewer treatment-related adverse events when compared to chemotherapy. The 2021 National Comprehensive Cancer Network (NCCN) guidelines recommend pembrolizumab or nivolumab alone or in combination with ipilimumab as a first-line treatment option in patients with dMMR/MSI-H mCRC [31].

Despite these developments, ICI is ineffective in metastatic MSS-pMMR CRC, which accounts for most patients [32]. Nivolumab plus low-dose ipilimumab produced an objective response rate of 69% in a phase II CheckMate 142 study, and its efficacy justifies first-line dual ICI therapy in randomized study [33]. During the 2024 Gastro intestinal Symposium of the American Society of Clinical Oncology (ASCO), the research revealed the data of CheckMate-8HW (NCT04008030) study. The effectiveness of nivolumab + ipilimumab versus nivolumab monotherapy or chemotherapy (mFOLFOX-6 or FOLFIRI) with or without bevacizumab/cetuximab in patients with mCRC with high microsatellite instability (MSI-H) or mismatch repair-deficient (dMMR) phenotypes is assessed in this randomized, open-label phase III clinical trial. The findings demonstrated that in patients with metastatic colorectal cancer that had an MSI of high or mismatch repair defective, nivolumab plus ipilimumab decreased the probability of disease progression or death by 79%. This study assists doctors in determining the optimal course of treatment for their patients by defining the added benefit of nivolumab with ipilimumab in comparison to nivolumab alone.

Several monoclonal antibodies that react effectively to cancer have been approved by the FDA for the treatment of colorectal cancer (CRC), including cetuximab, bevacizumab, panitumumab, ipilimumab, and pembrolizumab. The clinical trials with ICI for CRC that have been finished are displayed in Supplementary Table 1. These are a number of combination treatment approaches that have demonstrated significant potential for enhancing patients' overall clinical results. There are still issues with the broad application of monoclonal antibodies (mAb) in CRC

treatment, despite recent advancements. First, in order to guide clinical, create individualized regimens, and benefit more patients, it is critical to determine the status of MMR/MSI, RAS, and BRAF before to CRC treatment as well as the mutation status. Second, it is impossible to overlook its safety profile as a new therapy approach with enormous promise. One of the research focuses is on ways to lessen treatments' adverse effects and patients' pain. In order to lessen the concentration and adverse effects of a single immunotherapy , doctors attempt to mix multiple medications. Third, in CRC, immunotherapy is used in conjunction with chemotherapy, ICI, and radiation therapy to maximize the therapeutic impact and minimize adverse effects. To maximize the utilization of mAbs in clinical practice, concerns such patient selection, biomarker identification, and resistance mechanisms need to be addressed. In conclusion, more people may benefit from treatment if ICI alters the therapeutic prospects of colorectal cancer.

Name	Target	Data for Launch	Types
Ipilimumab	CTLA-4	2011	For progressive microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR) CRC (in conjunction with nivolumab)
Nivolumab	PD-1	2014	For progressive microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR) CRC (in conjunction with ipilimumab)
Pembrolizumab	PD-1	2014	For unresectable or metastatic microsatellite instable-high (MSI-H) or mismatch repair-deficient (dMMR) CRC
Dostarlimab	PD-1	2021	For recurrent or advanced solid tumors with mismatch repair deficiency (dMMR)

Table 1: The data of clinical trials with ICI for CRC.

Adoptive Cells

Adoptive cell therapy (ACT) is another term for cellular immunotherapy used to treat cancer. To eradicate cancer, this form of immunotherapy involves genetically modifying the body's immune system cells to express a CAR or a T-cell receptor (TCR) [33]. The therapy of numerous tumor has benefited greatly from the use of ACT. ACT is superior to other cancer immunotherapies in several ways. It is possible to cultivate large numbers of antitumor T cells in vitro, and their affinity for antigens can boost autoimmunity [34]. As TIL research progressed, cells with anticancer activity were extracted from melanoma patients' tumors and demonstrated promising treatment outcomes. TILs derived from the majority of CRC tissues do not seem to be able to identify tumor antigens, even when similar methods are used. Techniques for introducing anticancer TCRs into autologous lymphocytes for therapeutic use were developed as a result of further ACT use [35]. To increase antitumor activity, CARs with antitumor specificity can be injected into healthy lymphocytes [36]. By reprogramming a patient's own T cells to consistently produce CAR through gene transfer technology, CAR T-cell therapy combines antibody specificity with the powerful cytotoxic and memory properties of T cells [37]. CD19-targeted CAR T cells demonstrated complete response rates of roughly 90% in patients with relapsed or refractory acute lymphoblastic leukemia and

produced complete sustained remissions in populations of patients with refractory B-cell malignancies in early-phase clinical trials.

CAR T cell: A tailored therapy that has shown remarkable success in treating hematological malignancies, chimeric antigen receptor T (CAR T)-cell therapy is a significant therapeutic advancement for cancer research. CAR T treatment genetically alters autologous T cells and separates patient lymphocytes from peripheral blood. Through the use of lentiviral vectors or retroviruses, T cells can be genetically engineered to produce particular tumor antigen receptors in vitro. Independent of MHC, modified T cells are able to recognize malignant antigens and generate a particular anticancer immune response [38]. To attack tumor cells directly, CAR T cells release granulin B and perforin after rerouting to the tumor surface antigen and expressing synthetic receptors. Endogenous immune cells accomplish the goal of tumor treatment by releasing cytokines, which destroy tumor cells. To achieve a particular long-term anticancer effect, CAR T cells can develop into immunological memory T cells [39]. CAR T technology has advanced quickly in recent years, and new production techniques and transformational approaches have progressively improved CAR T's stability and efficacy while lowering prices and adverse effects. The CAR consists of hinge regions, transmembrane regions, an intracellular domain that mediates T-cell activation, primarily through the CD3 ζ signaling chain, and a target-binding extracellular region with antigen specificity, typically based on antibody fragments from a single-chain variable region (scFv) [40]. Six CAR T-cell products have been approved globally since the first generation, and countless more are undergoing preclinical and clinical testing. Production of CAR T-cells has been optimized to the fifth generation. The fifth generation of CAR T is employed for large-scale manufacture and treatment in an effort to overcome individual constraints [41,42].

Many researchers are investigating CRC modification techniques since CAR T-cell immunotherapy is a very promising anticancer treatment. To assess the effectiveness, safety, dosage levels, and maximum tolerable dose of CAR T cells against different overexpressed molecular targets in colorectal cancer, a few preclinical and clinical investigations are still in the initial stage (phase I/II clinical trials). CEA and NKG2DL were the most commonly employed targets in CAR T-cell therapy in CRC research, followed by EGFR and HER-2. A phase I increase in CAR T treatment dosages targeting CEA mCRC was carried out in 2017. The findings showed that two patients experienced considerable tumor decrease and two patients had stable illness for over 30 weeks [43]. Additional clinical trials are needed to confirm whether these results indicate a positive therapy impact and can be applied to all patients.

As cell technology advanced, scientists started testing different CAR immune cells and even the combination of several immunological techniques instead of concentrating on T cells. To improve the tumor response of natural killer (NK) cells, researchers fused the extracellular domain of their cell receptor NKG2D with DAP12 in 2019. A pilot clinical trial (NCT03415100) was carried out after the preclinical trial shown positive therapeutic effects in mice with colorectal cancer tumors [44]. NKG2D CAR-NK cells have the ability to recognize tumor cells and

demonstrate antitumor effector actions in patients with mCRC, according to preliminary verification. To manage graft-versus-host disease (GvHD), researchers developed CYAD-101 in 2020 by combining NKG2D-based CAR with non-gene-edited peptide-based technology (TIM) [45]. Preclinical results demonstrated that, even in the absence of induced GvHD, CYAD-101 retained its CAR-directed anticancer efficacy. 15 patients with refractory mCRC who had previously failed at least first-line treatment with oxaliplatin were included in a phase I alloSHRINK clinical trial (NCT03692429), which revealed 2 patients in partial remission and 9 with stable outcomes. This study, which was presented at the American Society of Clinical Oncology Gastrointestinal Cancer Symposium 2021 (ASCO-GI), showed how allogeneic CAR T-cell therapy attempted to get around the drawbacks of autologous CAR T. Researchers were able to target PD-1, TAM, and MDSC all at once in 2023 by secreting bispecific PD-1-TREM2 scFv antibodies into the tumor microenvironment (TME). CAR T cells for BsAb PD-1-TREM2 scFv secretion were demonstrated to have a greater antitumor potential in the CRC animal model [46]. The development of CAR T-cell therapy for solid tumors has stalled, despite the remarkable success of CAR T-cell therapy in hematological malignancies, especially CD19-positive B-cell malignancies. This study creatively combined CAR T cells and BsAb into a single immunotherapy platform with greater antitumor efficacy in tumor-bearing mice, inspiring new research for the study of CAR T [47]. Basic research in this area is being advanced by ongoing efforts; some studies have advanced to clinical trials, and several combination techniques have been proposed to further increase safety and efficacy. Every method has a different way of working and has its own set of benefits and drawbacks. Numerous intriguing therapeutic approaches have been put forth and shown effective in preclinical models, and a range of targets are available for CAR treatment of colorectal cancer. Numerous investigations have shown the critical role CAR treatment plays in solid tumors [48]. Apart from T cell engineering, NK cells have been contemplated as a substitute delivery system for CAR constructions and are believed to be less vulnerable to GvHD. Allogeneic CAR therapy and the therapeutic range of solid tumors can be extended by CAR-NK cells [49]. regulation methods should ideally enable the quick regulation of CAR T-cell activity, as CAR-related toxicity frequently manifests acutely [50].

Among ACTs, CAR T cells are one of the most researched and promising approaches. Clinical trials are still in their early phases, but the results have indicated encouraging therapeutic outcomes. During the study, some obstacles and constraints need to be addressed. First, one significant drawback of CAR T-cell treatment is the TME. The TME exhibits increased acid products from hypermetabolism, local tissue hypoxia, and problems with nutrition metabolism. These elements limit the inhibitory effect of CAR T cells on tumors and have an impact on T-cell survival, proliferation, and activation. It is still necessary to investigate whether customized CAR T cell modifications, such as integration with antitumor cytokines, inoculation technique, and dose control, can lessen the effect of the TME. Second, CAR T-cell therapy may have a number of harmful side effects. Cytokine release syndrome (CRS), which is the cytokine secretion reaction caused by CAR T-cell infusion and results in other systemic toxicities, is one of the most prevalent. Even in a little amount of time, patients may experience potentially fatal pulmonary circulation abnormalities, liver dysfunction, gastrointestinal reactions, and neurotoxic

reactions. Additionally, researchers are always working to reduce side effects and help more people with colorectal cancer. Because tissue-specific vascularization can hinder the proper biodistribution, concentration, and persistence of CAR T cells in afflicted organs, the selection of CAR T cells should also be tailored to the type of target tumor [51]. Positive clinical trial outcomes are now anticipated to give this new cell-based treatment hope.

Lymphocytes infiltrate tumors: In order to increase the immune activity and prevent tumor progression, TILs, an ACT, are reinjected into the tumor microenvironment after removing immune cells from tumor tissue and boosting their antitumor vitality *in vitro* [52]. With CD4+ and CD8+ subpopulations, TILs typically reflect a diverse population of αβ T cells found in the TME. Following amplification, these cells develop into killer cells that express the apoptosis inducer FASL and release perforin. Perforin facilitates the granzyme's entry into the cell by rupturing the cell membrane. The tumor cells will thereafter experience apoptosis as a result of the cleavage of caspase precursors [53]. Selecting the right type of TILs is especially crucial because the distributions of TILs vary throughout TME types. In order to screen for TILs for cancer treatment, researchers are attempting to investigate the connection between TILs and rehabilitation. However, individual differences affect TIL product generation and responsiveness to solid tumors [54,55]. TILs may be a significant predictive factor for peripheral or infiltrating colorectal cancer, according to studies [56,57]. Research has demonstrated that CD8+ T-cell infiltration in the CRC TME was consistently greater than CD4+ T-cell infiltration and was linked to a better prognosis in CRC. By identifying tumor-associated antigens (TAAs) and eliminating altered cells directly, CD8+ TILs mediate the tumor rejection response [58]. To increase the cytotoxic ability of CD8 TILs to target the tumor cells, effector CD8 T cells in the TME generate IL-2, IL-12, and IFN-γ [59].

Since colorectal cancer (CRC) has less TILs than other types of cancer, one of the issues with using TILs for CRC treatment is gathering and treating more TILs [60]. For the T cell rapid expansion protocol (REP), researchers are currently employing the conventional collection and *in-vitro* expansion techniques. To create a single-cell suspension, tumors are removed from the patient while under anesthesia and either chopped into tiny pieces or broken down enzymatically. For 3–5 weeks before REP, tumor fragments are cultured alone with high-dose IL-2 (6,000 IU/mL). Then, for 5–6 weeks, the pure lymphocyte cultures that were chosen will be co-cultured with lymphocytes and tumor cells in the presence of irradiated feeder lymphocytes (an antibody that targets the ϵ subunits in human CD3) and IL-2 to rapidly expand. After that, the patient will receive a cell transfusion.

An in-vitro amplification model for TILs has been successfully created by researchers [61]. Twelve patients who were having primary colorectal cancer surgery had their tumor tissues removed for pathological analysis and then placed in a one-time perfusion bioreactor with an IL-2 and IL-12 starting medium. An important step in the immunotherapy of TILs was taken when the amplified TILs demonstrated high functional potential by measuring non-specific stimulation (interferon-γ, tumor necrosis factor-α cytokine assay), which revealed that the expanded TILs were primarily composed of (73%) the ACT-relevant CD3+/CD8+ effector memory phenotype (CD45RO+/CCR7).

One of the challenges in TIL therapy is figuring out how to increase effector T cell numbers more effectively and enable them to have an anticancer effect. Preclinical research has demonstrated that in early isolated TIL culture, CD8-dominated TIL generated a greater antitumor capacity when anti-4-1BB and CD3 antibody agonists were used [62]. In a phase II trial (NCT03610490), this single-center TIL was used to treat patients with OVCA, PDAC, and CRC who were not responding to conventional treatment. According to the data, the median PFS and OS were 2.53 months and 18.86 months, respectively, and the DCR was 62.5% but the ORR was 0%. The effectiveness of TIL in comparison to conventional second- or third-line therapy options in various cohorts could not be determined by the single-arm research. Nonetheless, the experiment's findings demonstrated how TIL treatment inhibits solid tumors. To determine the host factors linked to TIL treatment resistance, more research is required.

TILs have shown promising outcomes in recent years and are crucial in locating and eliminating target tumor cells. The development process still faces numerous obstacles, though, including treatment safety, a protracted production cycle, high production costs, manufacturing process optimization, and the application of cutting-edge genetic modification techniques to produce TIL cell therapies that are more effective. The development of side effects both on and off the target, such as CAR T-cell-associated encephalopathy syndrome (CRES), extratumoral effects, and acute respiratory distress syndrome as a result of targeted humoral recognition and killing, has been linked to a number of TIL/CAR T-cell trials that have raised safety concerns [63]. Moreover, the most frequent adverse effect of CAR T treatment is CRS [64]. Even while most adverse events can be well managed with prompt pharmacologic intervention, ACT can have long-lasting side effects [65]. On the other hand, somatic mutation-driven tumor-restricted expression of neoantigens guarantees the therapeutic development of cellular therapeutic reactivity against these antigens, which is thought to be the best and safest treatment option for ACT. This is independent of normal tissue damage. However, as technology continues to develop and expand, it is probable that additional TILs may be created that will give CRC sufferers hope.

Viral Oncolytic Treatment

OVT chooses a tiny virus as the viral vector with chimeric anticancer genes and immune components to boost the targeting and immunological activity. Oncolytic viruses (OVs) can target tumor cell growth by infecting the cells via cell carrier transport, intratumoral administration, or intravenous treatment. Tumor-related antibodies or immune factors are released throughout the value-added process in order to directly cause oncolysis, trigger the immune response, and attract immune cells to the tumor microenvironment (TME) in order to stop tumor growth [66,67]. Antiviral reactions are triggered by the release of antiviral cytokines, particularly interferons, which excite CD8 T cells and NK cells and encourage the development of APCs like dendritic cells (DC). Viral offspring, DAMP (containing host cell proteins), PAMP (viral particles), and TAAs will be released into the TME as a result of the lysis of the infected tumor cells [68,69]. Other tumor cells nearby or farther away will be infected by the virus's progeny. DAMPs and PAMPs activate receptors to boost the immune system. To trigger antigen-specific and virus-specific CD8 T-cell responses and, ultimately, to establish an immunostimulatory milieu, APCs ingest

TAAs and neoantigens [70]. VEGF function will be blocked, and VEGF antibodies will be released into the TME if the OVs are chimeric with VEGF antibodies. Consequently, local blood perfusion will be decreased, and tumor-nourishing arteries will be obstructed, depriving tumor cells of the oxygen and nutrients they require to flourish. One of the most promising immunotherapies for colorectal cancer is OVT. Since OVT has produced positive outcomes at the cellular and organismal levels in recent years, clinical trials are becoming a more important area of study. The poxvirus, reovirus, herpes simplex virus (HSV), and adenovirus are now the most often utilized viruses for OVT research. To play an oncolytic function in the multiplication or metabolism of OVs, certain tumor suppressor genes or antibodies that improve immune response are converted into viral DNA [71]. Researchers have attempted to employ OV technology to target the human 5T4 gene, CEA, PD-1, and CTLA-4 to treat colorectal cancer. In preclinical studies, OV modification has demonstrated a positive therapeutic impact and is anticipated to offer a novel therapeutic approach for the clinical management of colorectal cancer [72].

The trophoblast glycoprotein is the name given to the human 5T4 gene. It expresses a 72 kDa heavy N-glycosylated protein and is found at 6q14.1. Although 5T4 is infrequently expressed in normal tissues, it is extensively expressed in human trophoblast cells and the majority of malignancies [73]. To use chemotherapy to treat inoperable mCRC, researchers altered the vaccinia Ankara-5T4. Cyclophosphamide's ability to enhance the therapeutic potential of modified vaccinia Ankara-5T4 immunotherapy was assessed in this patient-centered, randomized phase I and phase II clinical trial. When administered MVA-5T4 or cyclophosphamide, the included patients had improved tumor control effects [74]. Despite not improving MVA-5T4's immunogenicity, cyclophosphamide has been shown to have a survival benefit and few side effects, necessitating more research.

The cell membrane is the primary site of expression for the CEA subgroup. CEA has been recognized as a significant indicator of colorectal cancer (CRC) and other cancers for over 50 years. Adenocarcinoma cells that produce CEA can be significantly inhibited by the CEA gene promoter constructs [75]. When the CEA promoter E1A (Δ24) and the ST13 tumor suppressor gene are inserted into an oncolytic adenovirus vector, the SW620 CRC xenograft cannot grow in naked mice and the mice's life period is extended [76]. A patent for the innovation has already been filed by a group of researchers (201110319434.4). To increase viral safety and encourage tumor-specific viral replication without lowering virulence, researchers created VG2025, a recombinant oncolytic herpes simplex virus type 1 (HSV-1) that leverages the dual control of transcription and translation (TTDR) of important viral genes [77]. While inhibiting viral replication in healthy tissues, VG2025 can effectively reproduce virally in CEA-positive cancer cells, encouraging oncolysis and the release of tumor antigens. Other tumor-specific promoters can be used in place of the CEA promoter in VG2025 as part of a larger platform to enable biomarker-based precision OVT.

OVT has shown encouraging outcomes in preclinical and clinical trials for colorectal cancer. The safety and specificity of OVs have been attained by advancements in molecular methods. Still, a number of obstacles prevented OVs from having the best anticancer action. In what ways are oncolytic viruses improved? The largest

obstacle is still delivering the OVs successfully, and the host's antiviral immunity must be taken into account [78]. OVs and ICIs together have currently shown potential in a number of clinical trials. It is anticipated that this approach will prove to be a viable treatment option for colorectal cancer.

CONCLUSION

Immunotherapy is a therapeutic strategy that boosts or activates the immune system to prevent tumor growth by using different cytokines, antibody medications, OVs, and immune cells [79]. More than 100 mAb products with notable therapeutic efficacy have been licensed by the FDA since the first mAb was approved [80]. Enhancing the accuracy of targeted treatments and minimizing side effects while successfully eradicating tumor cells is the ultimate objective of many tumor immunotherapies. The evolution of OV treatment, TILs, cell therapy, and ICIs in CRC is covered in this overview. The mechanisms of a number of immunotherapies are explained, and current immunotherapy research is presented for CRC patients in an effort to give them hope for a successful outcome and to provide researchers fresh ideas for future studies.

Improved survival and a lower chance of recurrence have been linked to high infiltration of particular subsets of immune cells in the immunological microenvironment of type I CRC in patients with stage I/II CRC [81]. Nonetheless, a number of cohorts have revealed a substantial mortality risk for patients with MSS CRC. The MSI/MSS subtyping has altered the way that colorectal cancer is diagnosed and treated. The combination chemotherapy regimen (FOLFOX) [(fluorouracil, 5-FU), oxaliplatin (oxaliplatin), and folic acid (folinic acid)] is less effective (up to 73.6% insensitive) in patients with MSI-H because they are in fact insensitive to fluorouracil treatment [82]. Consequently, it seems that determining a patient's microsatellite status before to CRC treatment is quite helpful in directing treatment classification.

The field of immunotherapeutic drugs' application in solid MSI-H cancers is changing quickly. While several approaches are being studied, most of them involve combining anti-PD(L)-1 drugs with other immunomodulators. To present, the only combination that has demonstrated improved survival in patients with MSI-H malignancies is anti-CTLA-4 with anti-PD(L)-1 [25]. There is uncertainty regarding the best time to administer immunotherapy, the length of time immune agents should be administered, the right dosage of immune medications, the combination approach of preoperative immunotherapy, and the cytotoxic characteristics of these medications [83]. It seems more optimal to use a short-course radiation treatment paradigm prior to CRC surgery, followed by four to five rounds of anti-PD1 therapy in conjunction with fluorouracil or its derivative chemotherapy [84]. While some patients with MSI-H/dMMR CRC do not benefit from ICI treatment, other patients with MSS/pMMR can experience a favorable clinical response from immunotherapy; hence, screening for individuals who can benefit from immunotherapy is still based on MSI/MMR status [85,86]. The potential of immunotherapy has started to emerge with the development of anti-PD-1 treatments that target the MSI-H:dMMR patient population, such as pembrolizumab and nivolumab [87]. Finding novel biomarkers to forecast the effectiveness of immunotherapy and

potentially the effectiveness of particular immunotherapy medicines is also critically needed in MSI-H cancers. Modern tools like spatial transcriptomics, high-parameter flow cytometry, and scRNA-seq have completely changed our knowledge of anticancer immune responses. These methods could give us crucial information on how immune cells behave in the TME as they develop and are used more frequently in the future. Using this information, more potent immunotherapies can be created.

It is anticipated that tumor immunotherapy will be the last tumor treatment technique and has emerged as the primary development direction and trend in tumor therapy. However, a number of factors, such as the development of compensatory inhibitory mechanisms that adversely affect the antitumor immune response and result in acquired resistance, restrict the effectiveness of these immunotherapies. The development of new technologies, the investigation of signaling pathways, and the hunt for novel tumor targets are all ongoing. These treatments may provide hitherto unidentified dangers to patient safety and public health because of their innovative, intricate, and technical nature. The danger of OV vaccines, TIL cell treatment, CAR T therapy, and ICI therapy was deemed to be low to moderate. Bioactive materials utilized in production, such as antibodies, cytokines, sera, growth factors, and antibiotics, as well as hazards to the product's stability and viability during freezing, thawing, storage, and cold chain transportation, are examples of potential risk factors. Furthermore, the product itself may have intrinsic dangers, including the inability to completely eradicate tumor cells or other undesirable cells, as well as possible issues or decreased product activity related to migration, proliferation, transplanting, and homing. In an attempt to lower the concentration of each individual drug and to lessen unpleasant drug reactions, researchers have attempted to combine many drugs; they have also produced positive experimental outcomes. Some studies have demonstrated the superiority of combination therapy. Apart from various immunotherapy combinations, immunotherapy in conjunction with chemotherapy, radiation, or other medications has been investigated with an emphasis on enhancing effectiveness, reversing resistance, and mitigating side effects. To sum up, immunotherapy is presently the most promising therapeutic approach and is anticipated to be a novel therapeutic approach for CRC patients.

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