Novel insight into the role of immunotherapy in gastrointestinal cancer (Review)

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Received July 12, 2022; Accepted September 30, 2022

DOI: 10.3892/mco.2022.2590

Abstract. To date, great progress has been made in studying the immunology of cancer and the development of immunotherapies. Immunotherapy has become an effective clinical strategy for cancer treatment in courtesy of its unique features. It has been demonstrated to delay tumor progression, reduce tumor recurrence and metastasis, and even cure tumors through enhancing the immune response, stimulating tumor-specific immunity and breaking immune tolerance. Several different immunotherapeutic approaches and methods are in the process of being developed, including the use of cytokines, immune checkpoint inhibitors, engineered T cells (such as T-cell-receptor T cells and chimeric antigen receptor T cells) and cancer vaccines. Digestive system neoplasms pose a serious threat to human health, including esophageal cancer, gastric cancer and colorectal cancer, and immunotherapy is considered to be a promising new avenue for the treatment of digestive system neoplasms. However, certain challenges remain in terms of the broad implementation of immunotherapies due to the incompletely understood mechanisms underlying tumorigenesis. Therefore, it is crucially important to understand both the various different types of immunotherapy and the immune landscapes in digestive system neoplasms in order to reduce the side effects associated with these therapies. The present review discusses existing and newly emerging immunotherapeutic methods that may be applied in the treatment of digestive system neoplasms and how their clinical efficacy may be enhanced.

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Key words: immunotherapy, gastrointestinal cancer, immune checkpoint inhibitors, chimeric antigen receptor T cells, vaccines

Contents

1. Introduction

Cancer immunotherapy is a type of cancer treatment that uses artificial stimulations to trigger the immune system's inherent ability to fight cancer. Following surgery, radiation therapy, chemotherapy and targeted therapy, cancer immunotherapy has emerged as the 'fifth pillar' for cancer treatment (1,2). There are generally two types of cancer immunotherapy: Passive and active. Passive immunotherapy is the use of immune system components, such as monoclonal antibodies (mAbs) generated outside the body, to stimulate the immune response, immunological memory and long-term response. By contrast, active immunotherapy, including the use of cancer vaccines and engineered cell treatments, comprises the direct activation of the immune response, immunological memory and long-term response utilizing components of the patient's immune system to stimulate an immune response (3,4).

Over the past few decades, numerous immunotherapeutic strategies have become established pillars of cancer treatment, seeking to boost the immune system to recognize specific antigens of cancer cells for their selective elimination, including cytokines, immune checkpoint inhibitors, engineered T cells such as T cell receptor (TCR) T cells and chimeric antigen receptor (CAR) T cells and cancer vaccines. Several of these

have demonstrated promising effects with respect to gastrointestinal cancer. Immune checkpoint blockade therapies use antagonists to block immune-inhibitory pathways, such as the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein-1 (PD-1)/programmed death-ligand-1 (PD-L1) pathways, and this type of therapy has been demonstrated to be one of the most effective strategies for treating various cancers in the clinic, including gastric cancer and esophageal cancer (5,6). Cancers may become treatable, or even curable, in the future, courtesy of immunotherapy (6,7).

The present review offers a brief introduction to several types of tumor immunotherapies, highlighting their clinical status, benefits and drawbacks. Subsequently, the review examines several of the new delivery systems that have been created to help with the clinical translation of immunotherapies. The overall purpose of the present review is to provide novel insight into the current status of immunotherapies in the treatment of various types of digestive cancer.

2. Therapeutic strategies of immunotherapy for cancer

It is well documented that the occurrence of cancer is due to a loss of the capability of the immune system to recognize and kill malignant cells (8). Cancer immunotherapy refers to a series of processes that are able to enhance the immune system, inducing or restoring the function of cytotoxic T cells or other immune effectors to kill malignant cells (Fig. 1). Cancer immunotherapy, a ground-breaking treatment method, attempts to stimulate or increase the body's own immune systems to detect and kill cancer cells (9). As a result, cancer immunotherapy has attracted a lot of interest due to its proven efficacy and lower toxicity compared with standard types of chemotherapy or other treatments that kill cancer cells directly (9). In general, immunotherapy is widely acknowledged as a promising approach for treating, or perhaps curing, certain types of cancer (10).

On the one hand, the immune system may shield the human body against the occurrence of cancer. However, the immune system is not able to exert any scavenging effects on low-immunogenicity tumor cells. The monitoring function of the immune system on tumor formation is a dynamically balanced process, which is called immune monitoring or immune surveillance (11-14). Herein, the immune system monitors the body for tissue damage, pathogen invasion and foreign substances. The immune system initiates a complex inflammatory cascade to eliminate damaged cells, to re-establish tissue homeostasis and to provide a memory of the invasion when a subsequent threat is recognized (5,12,14). Resulting from immune surveillance, the mechanisms of immunosuppression and immune activation are triggered simultaneously. In general, the innate immune system is limited to releasing cytokines and recruiting immune cells to initiate non-specific immune responses, whereas the adaptive immunity system directly recognizes and kills cancer cells due to its ability to specifically identify antigens present on the cancer cells (14,15). Numerous immunotherapeutic strategies have become important choices for cancer treatments, including cytokines, immune checkpoint inhibitors, engineered T cells such as TCR-T and CAR-T cells, and cancer vaccines (3,13,15).

3. Immunotherapy in esophageal cancer

In recent years, cancer immunotherapy has been indicated to be a potential new therapeutic option for esophageal cancer. Various preclinical or clinical trials of esophageal cancer immunotherapy, including immune checkpoint blockade, tumor vaccination and adoptive T cell treatment, are in the process of being conducted (16). Furthermore, immune checkpoint inhibitors, including an anti-CTLA-4 mAb (iplimumab) and anti-PD-1 mAbs (nivolumab and pembrolizumab), have been indicated to produce substantial tumor shrinkage and to increase the overall survival (OS) rates of patients with diverse types of cancer, findings that have aroused a new enthusiasm for immunotherapy for cancer (17).

Immune checkpoint inhibition has already been employed in the treatment of melanoma, and its efficacy in other types of cancer, including gastrointestinal malignancies, is currently being investigated (18). High PD-L1 expression levels are documented to be associated with a prolonged survival rate in patients with esophageal squamous cell carcinoma (ESCC; low, 41.9%; high, 84.5%). However, another study suggested that the membranous/cytoplasm PD-L1 expression was associated with tumor invasion depth and was an indicator of poor OS in patients with esophageal cancer; the P-vale of the association of the expression of PD-L1 with patients' OS was at the statistically significant threshold (0.0452), indicating the conclusion should be validated in large cohorts of patients (19,20). The expression of PD-L1 has been reported to promote the exhaustion of T cells and drugs that target PD-L1 may provide an effective approach for treating patients with ESCC who have high expression levels of PD-L1 (21). Pembrolizumab, a PD-1 inhibitor, is the first immune checkpoint blockade drug to have been approved by the Food and Drug Administration (FDA) for the treatment of advanced or unresectable melanoma (22). Recent studies have indicated that pembrolizumab may be used as the second-line treatment of chemotherapy for refractory PD-L1-positive gastric/gastroesophageal junction cancer. Ipilimumab, an immune checkpoint inhibitor, was demonstrated to boost the immune system via targeting CTLA-4 (23-25). In a pre-clinical model, the combination of ipilimumab and nivolumab has been indicated to elicit a synergistic effect. Several studies have demonstrated the safety and effectiveness of using a combination of nivolumab and ipilimumab in patients with advanced ESCC, confirming that combination treatment is more effective than nivolumab monotherapy. Numerous clinical trials are currently in progress to combine the inhibitory effects of CTLA-4 and PD-1; however, compared with PD-1/PD-L1, the side effects of CTLA-4 blockade are generally more common and severe. In view of this, novel strategies are being developed to mitigate these serious adverse events (26).

In spite of the fact that numerous clinical cancer vaccine trials have been performed in ESCC (27-31), regrettably, clinical trials of peptide-based cancer vaccines for ESCC have yet to be licensed for clinical use. However, in previous studies, researchers have identified that TTK protein kinase (TTK), lymphocyte antigen 6 family member K (LY6K), insulin-like growth factor 2 mRNA-binding protein 3 (IGF2BP3) and NUF2 component of NDC80 kinetochore complex are able to serve as novel immunogenic cancer antigens (ICAs) (30,31).

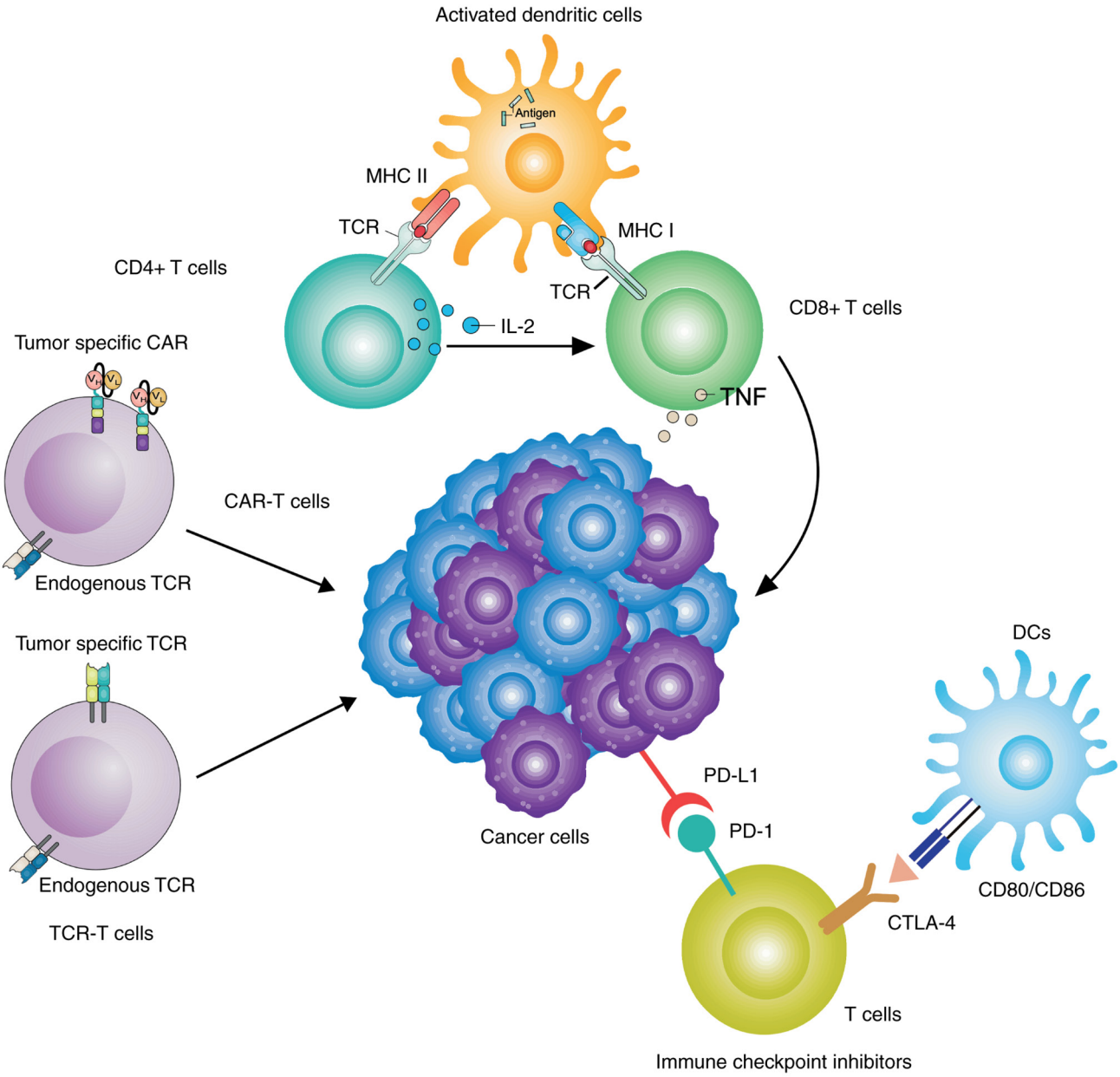

Figure 1. Major immunotherapeutic strategies for gastrointestinal cancer. Neoantigens, including proteins/peptides and tumor lysates derived from gastrointestinal cancer, may be loaded into DCs, and neoantigen-specific genes may also be transduced into DCs by using viral and non-viral vectors. DCs with loaded neoantigens may be cultured *in vitro* for maturation by providing additional signals and the APC function of these DCs results in enhanced CTL effector function, not only in terms of the number of cells, but also in terms of their activity. The optimizing APC function of DCs may induce $CD4^+$ T cells to become T helper cells, which results in further killing of the tumor. Tumor-specific $CD8^+$ T cells are directly harvested from gastrointestinal cancer and then transfected with CAR. Subsequently, the engineered $CD8^+$ T cells are allowed to proliferate *in vitro*, prior to being re-injected into patients for antitumor activity. ICIs function in terms of blocking T-cell inhibitory pathways through reactivating immune system-targeting cancer cells. The two major checkpoint inhibitors on T cells that block effector function are PD-1 and CTLA-4, which interact with PD-L1 expressed by cancer cells and CD80/86 expressed by APCs, respectively. Recent immunotherapeutic approaches using monoclonal antibodies that block the inhibitory interactions between cancer cells and other cells to improve CTL function have also been used in clinical practice. DC, dendritic cell; APC, antigen processing cell; CTL, cytotoxic T-lymphocyte; CTLA-4, CTL-associated antigen 4; ICI, immune checkpoint inhibitor; CAR, chimeric antigen receptor; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand-1.

These ICAs are highly and frequently expressed among different esophageal cancer antigens, and as they have been demonstrated to be associated with the survival and cell proliferation of ESCC, they may be anticipated to be used as cancer vaccine targets for ESCC (30,31). Accordingly, there are three human leukocyte antigen (HLA)-A24-restricted immune-dominant peptides that were derived from TTK, IGF2BP3 and LY6K. In an HLA-A24 phase I/II clinical trial, the prognosis of patients with advanced ESCC who experienced a vaccination-induced immune response was improved compared with that of patients without an immune response (30).

For adoptive cell therapy (ACT), activated T cells are usually collected from cancer tissues or peripheral blood and the isolated T cells are subsequently activated via *in vitro* incubation with interleukin-2 before being reinjected into the

patient. Genetically modified T cells that deliver CAR or TCR into other T cells are another type of cell treatment. The goal of this therapy is to boost tumor-specific immunity (32). In 2000, the first ACT clinical trial for ESCC was conducted, wherein each patient was injected with $0.8x10^9$ cells once every 2 weeks. Of note, four of the eleven patients exhibited considerable tumor shrinkage and few side effects were observed (33). The first human clinical trial of TCR-T cell treatment was performed in patients with ESCC who expressed melanoma-associated antigen 4. Of these patients with ESCC, seven exhibited significant disease progression after having received treatment for 2 months; however, three patients with the smallest lesions lived for over 27 months following therapy, indicating the potential effectiveness of TCR-T cell therapy (34).

Clinical trials have confirmed the great potential of immunotherapy in esophageal cancer. The combination of immunotherapy with existing or new treatment methods is expected to offer the best treatment strategy for esophageal cancer (35). The high incidence of neoantigens and radiosensitive tumors, and detection of numerous ICAs in ESCC, are factors that improve the prospects for immunotherapy. Combining immunotherapy with other therapies (including chemoradiotherapy and targeted therapy) may prove to be an appropriate and realistic therapeutic approach for ESCC (32).

4. Immunotherapy in gastric cancer

Tremelimumab is a humanized CTLA-4 mAb that was found to be effective in treating patients with advanced gastric cancer (36). However, patients with advanced gastric cancer who underwent treatment with ipilimumab, another inhibitor of CTLA-4, did not reach the expected end-point (clinical trial no. NCT01585987). Ipilimumab treatment did not improve the progression-free survival (PFS) or OS rates of patients with gastric cancer following first-line therapy (37). To date, the FDA has approved three PD-1 inhibitors: Pembrolizumab, atezolizumab and nivolumab. The phase I clinical trial of patients with gastric cancer with nivolumab (clinical trial no. NCT01928394) has been completed and the preliminary results suggested that patients had an objective response, regardless of the status of PD-L1 (38). A randomized phase III trial reported on the outcomes of patients with advanced gastric cancer who underwent nivolumab treatment. The results demonstrated that nivolumab treatment led to improvements in the OS rate, PFS rate and objective response rate (ORR) in patients with advanced gastric cancer undergoing multi-line treatment; however, the differences were found not to be significant (39). Several clinical trials with anti-PD-L1 inhibitors such as durvalumab, atezolizumab and BMS936559 have also been conducted to evaluate their effectiveness in patients with gastric cancer (40) (Table I).

Gastric cancer may be classified into four molecular subgroups based on its genomic and transcriptomic characteristics according to The Cancer Genome Atlas, which exhibit different therapeutic responses to immune checkpoint inhibitors (41). The KEYNOTE-061 clinical trial (42) indicated that patients with gastric cancer with a combined positive score (CPS) ≥10 (i.e., CPS of PD-L1 expression) benefited most from second-line treatment with pembrolizumab. The KEYNOTE-061 study also suggested that patients with a high tumor mutation burden (TMB-H), i.e., TMB-H ≥10 mut/Mb, exhibited a higher ORR (40 vs. 13%) and a longer OS rate (not reached vs. 8.1 months) (42). The phase III KEYNOTE-062 trial (43) demonstrated that the median OS rate of patients with gastric cancer with mismatch repair or high microsatellite instability (MMR/MSI-H) who were treated with pembrolizumab plus chemotherapy reflected improved survival benefits compared with those who received chemotherapy alone. An analysis of patients with metastatic gastric cancer treated with pembrolizumab revealed that patients with gastric cancer who also had Epstein-Barr virus (EBV) infection had an ORR of 100% and the EBV infection status appeared to be a better biomarker for predicting response to pembrolizumab compared with MSI-H (ORR, 85.7%) or PD-L1 expression (ORR, 50%) (44). Considered altogether, it appears that patients with gastric cancer with positive PD-L1 expression, EBV infection, TMB-H or MMR/MSI-H may respond well to immune checkpoint inhibitor therapy.

Previous clinical trials have assessed the safety and effectiveness of cancer vaccines in patients with gastric cancer (45,46). Two vaccines using peptides derived from vascular endothelial growth factor receptors-1 and -2 were tested in patients with advanced gastric cancer. This vaccination, in conjunction with chemotherapy (S-1 combined with cisplatin), was able to successfully prevent vascular endothelial growth, resulting in prolonged OS times (47). However, in spite of these findings, numerous issues in the development of effective cancer vaccines remain unsolved, such as the identification of tumor-specific antigens and the development of vaccine delivery methods. A number of ACT clinical trials have demonstrated inhibition of gastric cancer progression (48,49). In addition, human epidermal growth factor receptor 2 (HER2)-based CAR-T cell therapy was investigated in pre-clinical trials, wherein human T cells were genetically modified to express CAR, which targeted the gastric cancer cell antigen HER2; i.e. the T cells were designed to target HER2-positive gastric cells (50). However, the safety and effectiveness of this new type of therapy require further investigation.

In conclusion, given that gastric cancer is characterized by high heterogeneity in complex host genetic and immunological settings, and given the high occurrence of somatic mutations in patients with gastric cancer, which has led to the suggestion that gastric cancer may be an attractive candidate for immunotherapy, gastric cancer is continuing to receive considerable attention in this regard. Specifically, numerous clinical trials have demonstrated promising results in terms of gastric cancer treatment, using either immune monotherapies or combination therapies including immune checkpoint blockade therapies, CAR-T cells and cancer vaccines, the latter of which have provided the most promising results in the treatment of gastric cancer (51).

5. Immunotherapy in colorectal cancer

Several therapeutic strategies have transformed the general strategy for treating patients with colorectal cancer in recent years, thereby markedly improving patient survival rates.

Table I. Clinical outcomes of immunotherapies of clinical trials on gastrointestinal cancer.

Drug class/study drug	Trial identifier no.	Investigator, year	Clinical setting	Therapeutic protocol	AJCC stage	Phase	Patients, n	Outcomes	(Refs.)
Anti-CTLA-4 antibodies									
Ipilimumab	NCT01585987	BMS, 2012	AGC/GJA	Ipilimumab vs. BSC	IV	II	57+57	PFS: 2.73 vs. 4.90 mo	(37)
Anti-PD-1 antibodies									
Pembrolizumab	NCT02178722	Mark Jones, 2014	MSI-H CRC/GC	Pembrolizumab	NA	II	16+27	ORR: 44/22% for MSI-H CRC/GC	(68)
Pembrolizumab	NCT02370498	Merck Sharp, 2015	AGC/GJA	Pembrolizumab vs. Paclitaxel	IV	III	296+296	OS: 9.1 vs. 8.3 mo; PFS: 1.5 vs. 4.1 mo	(42)
Pembrolizumab	NCT02494583	Merck Sharp, 2015	AGC/GJA	Pembrolizumab +SOC vs. SOC	IV	III	257+250	OS: 12.5 vs. 11.1 mo; PFS: 6.9 mo vs. 6.4 mo	(43)
Vaccine-based immunotherapy									
GI-6301	NCT01519817	James Gulley, 2012	CRC	Yeast-Brachyury vaccine (4, 16, 40, 80 YU dose)	NA	I	3, 3, 16, 9 for each dose	1, 1, 8, 7 patients with Brachyury-specific T-cell responses	(69)

ORR, objective response rate; OS, overall survival (median); PFS, progression-free survival (median); PD-1, programmed cell death 1; CTLA-4, cytotoxic T lymphocyte-associated protein 4; MSI-H, microsatellite instability-high; BSC, best supportive care; SOC, standard of care chemotherapy; CRC, colorectal cancer; AGC, advanced gastric cancer; GJA, gastroesophageal junction adenocarcinoma; AJCC, American Joint Committee on Cancer; NA, not available. All the results were obtained from the NCT website (https://clinicaltrials.gov/).

Of note, novel immunotherapies may change the colorectal cancer landscape (52). Similarly to the situation with gastric cancer, at present, three mAbs (pembrolizumab, nivolumab and ipilimumab) have been approved by the FDA for patients with metastatic colorectal cancer with MSI-H or deficiency of (d)MMR (53). Ipilimumab was the first drug designed to interfere with immune checkpoints (54). Other promising checkpoint inhibitors, such as anti-PD-1 mAb or PD-L1 mAb, are able to boost the immune response to recognize and kill cancer cells. These drugs are currently being evaluated in clinical studies, either alone or in combination. The European Society for Medical Oncology consensus guidelines (55) recommend the use of the MSI test, as this has high predictive value for checkpoint inhibitor usage in patients with colorectal cancer, implying that pembrolizumab may be used in patients with colorectal cancer with MSI-H. A previous clinical trial indicated that 11 patients with colorectal cancer with dMMR had relatively high ORRs and PFS rates, compared with 21 patients with proficient (p)MMR (ORR: 40 vs. 0%; and PFS: 78 vs. 11%). These results support the predictive value of the patients' MMR status in terms of making the most appropriate choice of immune checkpoint blockade therapy (56).

Currently, cancer vaccines, cytokines and androgen deprivation therapy are also being evaluated in different clinical trials. The majority of these immunotherapies are still at the pre- or early clinical trial stages, although their efficacy in other types of cancer has already provided some optimism in terms of their potential for colorectal cancer treatment. Deficiencies in DNA MMR protein may cause insertion or deletion mutations, which leads to MSI, resulting in the mutated peptide antigen. These antigens derived from mutations of the coding region of genes are thought to be highly immunogenic stimulants, making them ideal targets for developing cancer vaccines (57). However, clinical trials of therapeutic vaccines for the treatment of colorectal cancer based on different delivery approaches have elicited inconsistent results (58). For instance, 254 patients with colorectal cancer who underwent surgical resection were treated with active specific immunotherapy (ASI), comprising irradiated autologous tumor cells (59). The original study concluded that patients with stage II colorectal cancer had a high recurrence-free survival (RFS) rate, whereas no benefits in RFS were observed in patients with stage III colorectal cancer. However, in a recent retrospective analysis, 196 well-preserved tumor specimens were re-evaluated to assess the results associated with the MSI status [34/196 dMMR/MSI (17.3%)] (60). Patients who received ASI therapy were observed to have a high 15-year RFS rate compared with those who underwent surgery alone and this was independent of the MSI status and the American Joint Committee on Cancer stage. Compared with the patients with pMMR/MSS, the 15-year RFS rate of the patients with dMMR/MSI-H colorectal cancer was significantly higher (dMMR/MSI-H, 85% vs. pMMR/MSS, 64%).

The effectiveness and safety of adoptive T cell therapy was first assessed in three patients with refractory colorectal cancer (61). The patients were injected with TCR-T cells that targeted the carcinoembryonic antigen (CEA) epitope. A response was observed in terms of decreasing serum CEA levels in one of three patients, and the objective tumors were observed to have dissipated liver and lung metastasis. It is worth noting that all three patients exhibited severe transient inflammatory colitis. Furthermore, with the development of CAR-T cells, this novel technology has been expanded to genetically modify T cells such that they express target proteins presented on the cancer cells, thereby allowing the CAR-T cells to recognize and kill cancer cells (62).

Overall, the use of immunotherapy for colorectal cancer is developing rapidly. As our understanding of the immune system and its complexity grows, so does our ability to exploit its potential. Recognizing that one unique approach may not be usefully applied for each patient, efforts are being made to develop the immune system using traditional and novel therapies, thereby providing reasons for optimism for the future immunotherapy of patients with colorectal cancer.

6. Similarities and differences of immunotherapy in gastrointestinal cancer

Currently, immunotherapy for gastrointestinal cancer comprises immune checkpoint inhibitors, TCR-T cells, CAR-T cells, cytokines and cancer vaccines. Of these, the checkpoint inhibitors are the drugs that have been the most studied and approved for the treatment of gastrointestinal cancer. Vaccines, cytokines and adaptive cell transfer therapies have yet to be approved by the FDA for gastrointestinal cancer, although they are being investigated in clinical trials (63). The FDA-approved drug pembrolizumab has been used for the first-line treatment of patients with unresectable or metastatic dMMR/MSI-H colorectal cancer since 2020 (64). Subsequently, the FDA-approved drug nivolumab, in combination with certain types of chemotherapy, has been used for the initial treatment of patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer and esophageal adenocarcinoma since 2021 (65). The immune checkpoint inhibitors show promising therapeutic effects in all three types of gastrointestinal cancer that have been discussed in the present review.

However, the use of immunotherapy has been limited in the treatment of gastroesophageal cancer, compared with colorectal cancer, due to high tumor heterogeneity and the complex underlying immunosuppressive mechanisms (63). Immune checkpoint inhibition therapy has achieved certain successes in gastric cancer with high mutation burden, including EBV-positive gastric cancer (66). Furthermore, immunotherapy has been mainly limited to the treatment of either the advanced stage of the malignancy or the treatment of refractory gastric or esophageal cancers (67). For the treatment of gastric or esophageal malignancies, immunotherapy has also been combined with certain types of chemotherapy to obtain a better prognosis for patients with gastric or esophageal cancer (65). Novel biomarkers, and the rational threshold of current biomarkers, for immunotherapy remain to be investigated in order to expand the scope of their applicability in gastric and esophageal cancer.

7. Conclusion

Gastrointestinal cancer is the most commonly occurring digestive system cancer type and associated with relatively

low survival rates due to inadequate therapies and aggressive features. Immunotherapeutic methods, including immune check point inhibitors, CAR-T cells, as well as cancer vaccines, have demonstrated great promise in terms of eliminating cancer cells through reactivating the immune system. Promising results of immunotherapy have been observed in melanoma, lung cancer and hematological malignant tumors. Anti-PD-1 antibodies have also achieved promising results with respect to gastrointestinal cancer, particularly in the case of ESCC. Combination therapies with other immunotherapeutic drugs, targeted therapies, chemotherapy and stroma-regulating drugs may provide treatment opportunities for patients with advanced gastrointestinal cancer. We remain hopeful that aggressive gastrointestinal cancer will become one type of chronic disease that is curable by different types of therapies in the future.

Acknowledgements

Not applicable.

Funding

This research was supported by a grant from the Outstanding Talents Start-up Grant of Xuzhou Medical University (grant no. D2021021).

Availability of data and materials

Not applicable.

Authors' contributions

YL, JC and QS conceived the idea for this review. QS directed the work. YL, JC and QS drafted the manuscript. YX participated in the discussion and QS revised the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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