Current immunotherapy in gastrointestinal malignancies A Review

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Accepted 9 December 2020
Published Online First 22 December 2020

To cite: Dahiya DS, Kichloo A, Singh J, *et al*. *J Investig Med* 2021;**69**:689–696.

ABSTRACT

Immunotherapy is an extremely important breakthrough and an exciting new modality of treatment for a wide spectrum of cancers. It is focused around developing agents to stimulate or suppress the immune system, in a specific manner, to fight off a wide spectrum of diseases, particularly cancers. Traditional therapies available for the treatment of cancers include surgical intervention, chemotherapy, radiation therapy or a combination of these, which tend to be very non-specific. However, immunotherapy shows a stark difference from conventional therapy, in fact, that it has a high level of specificity for the tumor-specific antigens. The recent success of cancer immunotherapies in clinical trials is slowly revolutionizing the landscape for cancer therapy. The US Food and Drug Administration has approved numerous agents, after clinical trials showed promising results, for the treatment of multiple cancers. The role of immunotherapy in gastrointestinal cancers has also been very promising, particularly in patients with advanced metastatic disease or malignancies refractory to initial treatment. In this review of literature, we detail and discuss the immunotherapy agents approved for the treatment of GI cancers and glance at the future of immunotherapy for patients with these cancers.

INTRODUCTION

Around the globe, the prevalence of different subtypes of cancers is on the rise and is one of the leading causes of disability, morbidity, and mortality. Most cancers are heterogenous both on histology and pathology, and are usually caused by the accumulation of variations in the genome that control normal cell physiology. Due to a variety of factors or under the influence of carcinogens, normal cells can escape the cell cycle, gain infinite unregulated division potential and lead to the accumulation of monoclonal (similar genetic makeup) neoplastic cells. The main types of gastrointestinal (GI) cancers with significant disease burden in the USA include esophageal, gastric, pancreatic, hepatobiliary and colorectal cancers (CRCs). They can be further classified into different subtypes based on the predominant cell of origin. According to the statistics from the American Cancer Society (2014), among the GI tract cancers, CRC had the highest cancer-related mortality followed by pancreatic, gastric and esophageal cancers.[1] Over the last few decades, there has been a significant shift in trends for the treatment of GI cancers with the advent of immunotherapeutic agents. Immunotherapy is rapidly evolving into a separate therapeutic entity and a potential fifth pillar alongside other conventional treatment of cancers, such as surgical intervention, chemotherapy, radiotherapy, or targeted therapy.[2] Immunotherapy is touted to be more specific than conventional treatment modalities which lacked specificity despite combinations and has also been reported to improve overall survival and disease-free survival rates, particularly in patients with advanced metastatic disease or malignancy refractory to first-line treatment.[2 3] For cancers of the GI tract, immunotherapy consists mainly of immune checkpoint inhibitors (ICIs), vaccine therapies, cytokine, and adoptive cell transfer (ACT) therapy. In this review of literature, we discuss briefly the different types of GI cancers and their presentation. We also detail the current role of immunotherapy in the treatment of specific GI cancers, the efficacy and potential challenges clinicians may face with the treatment regimens, and possible future immunotherapy agents currently under evaluation in clinical trials. After promising results from some clinical trials, the US Food and Drug Administration (FDA) has approved numerous agents for the treatment of GI cancers, which are also discussed. In the near future, combination therapies, including combinations of immunotherapy or immunotherapy plus traditional therapies, may be the way to move forward for the treatment of all GI cancers.

DISCUSSION

GI cancers consist of esophageal, gastric, pancreas, hepatobiliary and CRCs. They are a major cause of morbidity and mortality worldwide and in the USA. The American Cancer Society collects and compiles data on the cancer burden, and the associated morbidity and mortality as a result of these cancers. According to the 2014 statistics from the American Cancer Society, CRC ranked at third place followed by pancreatic, gastric and esophageal cancers at fourth, fifth and sixth cancers, respectively, in

terms of cancer-related mortality in the USA.[1] Conventionally, the mainstay treatment for GI cancers has been focused around surgical intervention, chemotherapy, radiation therapy, antiangiogenic therapy or a distinct combination of these; however, the overall survival from GI tumors, despite the use of these combination therapies, remains poor.[2] Over the last couple of decades, trends have shifted to the introduction and use of a new treatment modality, namely, immunotherapy, for GI cancers to decrease morbidity and to improve mortality outcomes.[3] The US FDA has approved numerous, commonly used agents (table 1), discussed in this review under the cancer-specific section, for a magnitude of GI cancers after promising results in clinical trials. Investigators are consistently striving to discover new and more specific agents for the treatment of these GI cancers.

The concept of immunotherapy was first speculated in 1909 by Smith, who believed that the immune system could suppress the growth of carcinomas by recognizing the tumor cells as foreign antigens.[4] This led to the immune system becoming an area of great interest to scientific investigators mainly due to its specificity in targeting tumor-specific antigens. Immunotherapy is focused around developing agents to stimulate or suppress the immune system, in a specific manner, to fight off a wide spectrum of diseases, particularly cancers. Progress in the field is largely dependent on the identification of new immune-based targets, and a better understanding of the workings of the immune system.[5] For a purely GI perspective, immunotherapy has provided significant breakthroughs in improving the overall survival and increasing the disease-free survival rates, particularly for advanced metastatic disease and malignancies refractory to first-line therapy.

For GI cancers, immunotherapy consists mainly of checkpoint inhibitors, vaccine therapies, cytokine, and ACT therapy. ICIs are a class of antibodies that block the 'immune checkpoint' through three major pathways, which include the programmed cell death protein (PD-1), programmed death-ligand 1 (PD-L1), or cytotoxic T-lymphocyte associated protein-4 (CTLA-4). PD-1 acts as an immunological 'off switch' and hence, the presentation of the PD-1 receptor with PD ligand leads to evasion of apoptosis and potential for indefinite replication. Similarly, CTLA-4 downregulates the immune responses when bound, leading to development of cancers. ICIs revitalize the antitumor response through interruption of the coinhibitory signaling pathways and promote immune-medicated tumor cell lysis. However, like any therapy available, resistance to immunotherapeutic agents may develop. Several mechanisms which contribute to the development of resistance have been identified and can be divided into two subtypes, mainly tumor-intrinsic and tumor-extrinsic mechanisms. The common tumor-intrinsic mechanism includes downregulation of major histocompatibility complex (MHC), and genetic or epigenetic alterations (loss of B2M gene, loss of PTEN, or JAK, MAPK, PI3K, or WNT mutations).[6] Additionally, the common tumor-extrinsic mechanisms contributing to resistance include the interaction of the gut microbiome with the immunotherapeutic agents, changes in immune checkpoint expression, T-cell exhaustion and change in phenotype, recruitment of immunosuppressive cell population (T-regs, myeloid derived suppressor cells and type II macrophages), and release of cytokine or metabolites in the tumor microenvironment (colony stimulating factor-1, tryptophan metabolites, transforming growth factor-β and adenosine).[6]

Furthermore, other immunotherapies, such as vaccine-based cancer therapy, deliver a concentrated form of the tumor antigen to human leukocyte antigen class I and class II molecules of the antigen-presenting cells. This helps generate a specific CD4 and CD8 T-cell response which is antitumor in nature and leads to destruction of the tumor cells. Adoptive T-cell therapy is a form of passive immunization which can be achieved by the collection of activated T cells from the cancer tissue, stimulation in vitro with interleukin (IL)-2 and infusion back into the patient or genetically engineering T cells either by translocating chimeric antigen receptor T cell (CAR-T) or transducing antigen-specific T-cell receptor (TCR) into T cells (TCR-T cells). This leads to the formation of tumor-specific T-cells which can identify and eliminate cancer cells. These therapies are further discussed in our literature review in a tumor-specific manner. Additionally, table 1 summarizes immunotherapy agents for GI malignancies.

Esophageal cancers

Esophageal cancer is an aggressive, male predominant, largely fatal malignancy with a 5-year survival ranging from 15% to 20%.[7] The two predominant histological subtypes include squamous cell carcinoma (SCC), which is more common worldwide, and adenocarcinoma, which is the common subtype in Western countries corresponding to a rise in the incidence of Barrett's esophagus, obesity and gastroesophageal reflux disease (GERD).[8] Patients with esophageal cancers most commonly present with dysphagia, prompting the care provider for further investigation via an endoscopy and biopsy, which help to confirm the diagnosis. After the diagnosis is confirmed, the next step in management is to establish the clinical stage of the malignancy, which helps guide therapy. This is done with the help of CT or positron emission tomography (PET).

ICIs in esophageal cancers

SCC of the esophagus is associated with a high somatic mutation load, and hence, there is substantial benefit of PD-1 blockade in these tumors.[9] Nivolumab, a human monoclonal immunoglobulin (Ig)G4 antibody that binds PD-one expressed on activated T cells, showed promising activity in a an open-label, multi-centre, phase II trial.[10] Immunotherapy with nivolumab plus chemotherapy or radiation may be the way forward for the treatment of esophageal cancers. Adenocarcinoma of the esophagus, commonly seen in the United States, has similar treatment strategies as gastroesophageal junction (GEJ) adenocarcinoma and is therefore discussed in the next section.

Gastric cancers (GCs)

GC is also an aggressive, male dominant, fatal malignancy. However, due to significantly improved nutrition, food preservation, better prevention, earlier diagnosis and treatment, the incidence over the past few years has been steadily declining; however, literature still reports that GC carries a poor prognosis.[11] As per the 2014 American Cancer Society statistics, it was the fifth most common cancer in the USA.[1] About 95% of GCs are adenocarcinomas

Table 1 Immunotherapy agents for GI malignancies

GI malignancies	Immunotherapy
Squamous cell carcinoma of the esophagus	▲ ICI: nivolumab.
Gastric cancers	▲ ICIs: pembrolizumab and nivolumab. ▲ Adoptive T-cell transfer: under investigation.
Gastroesophageal junction adenocarcinoma	▲ ICIs: pembrolizumab and nivolumab.
Pancreatic cancers	▲ ICI: pembrolizumab, atezolizumab, and Ipilimumab. ▲ Vaccine-based immunotherapy: clinical trials ongoing for a combination of GVAX+CRS-207±nivolumab.* ▲ Indoleamine 2,3-dioxygenase inhibitor: indoximod. ▲ CCR2/CCL2 signaling pathway inhibitor: clinical trials ongoing for PF-04136309.
Hepatobiliary cancers	▲ ICI: nivolumab showed promising results, clinical trials ongoing for pembrolizumab, tremelimumab, ipilimumab, atezolizumab, avelumab and durvalumab. ▲ Vaccine-based immunotherapy: HEPAVAC project ongoing. ▲ Adoptive T-cell transfer: under investigation.
Colorectal cancers	▲ ICIs: pembrolizumab and nivolumab. ▲ Vaccine-based immunotherapy: clinical trial ongoing for talimogene laherparepvec local injection vaccine+atezolizumab. ▲ Adoptive T-cell transfer: chimeric antigen receptor T-cell therapy.

*GVAX: pancreatic cancer cell line that expresses GM-CSF; CRS-207: live-attenuated *Listeria monocytogenes* strain that expresses mesothelin.
GI, gastrointestinal; ICI, immune checkpoint inhibitor.

followed by primary gastric lymphomas. GC can be classified based on their anatomical location into cardia and non-cardia cancers.[12] Non-cardia cancers are usually associated with chronic gastritis, whereas the pathogenesis of cardia cancers is still unclear. The two proposed etiologies for cardia cancers include association with GERD resembling esophageal adenocarcinoma and association with *Helicobacter pylori* atrophic gastritis resembling non-cardia cancers.[13] Through histology, GC can be classified into two main types[14 15]:

1. Intestinal (well differentiated): more common and seen in older men, better prognosis.
2. Diffuse (poorly differentiated): less common and seen in younger individuals and frequently in women.

The early stages of GC may be asymptomatic or associated with non-specific symptoms such as dyspepsia. Advanced stages may present as persistent abdominal pain; anorexia; weight loss; hematemesis, if ulcerations are present; and persistent vomiting due to outflow obstruction.[16] The lack of specificity of the symptoms results in a delayed diagnosis and treatment. An upper GI endoscopy with biopsy is used to confirm the diagnosis, and CT or PET scan can be used to determine the stage, which may help guide therapy.[17]

ICIs in GCs

PD-L1 is overexpressed in GC and this higher expression is associated with an overall worse prognosis.[18] The KEYNOTE-012 trial (phase Ib), which evaluated the use of pembrolizumab in 36 patients with a positive PD-L1 profile in advanced or metastatic gastric or GEJ adenocarcinoma, demonstrated encouraging antitumor activity and a reasonable toxicity profile.[19] The FDA approved the use of pembrolizumab for previously treated patients with recurrent locally advanced or metastatic GC or gastroesophageal junction cancer (GEJC) whose tumors express PD-L1 after the success of the KEYNOTE-59 trial.[20] Nivolumab, a human monoclonal IgG4 antibody, was studied in the ATTRACTION-2 (phase III randomized and double-blinded) trial, which indicated its use as a new treatment option for heavily pretreated patients with advanced GC or GEJC.[21] Hence, it has been approved in Japan for the treatment of advanced or recurrent GCs that have progressed after chemotherapy. Many clinical trials are currently evaluating the efficacy and toxicity profile of the combination therapy with CTLA-4 and PD-1 ICIs.

ACT therapies in GEJ adenocarcinoma

Adoptive T-cell transfer is a form of passive immunization which can be achieved by[22]

1. Collecting activated T cells from the cancer tissue, stimulating with IL-2 in vitro and then infusing back into the patients.
2. Genetically engineering T cells, translocating CAR-T or transducing the antigen-specific TCR into T cells (TCR-T cells).

The main aim was to improve tumor-specific immunity. Many trials have shown that the persistence of T cells was responsible for the regression of tumors; therefore, the major obstacle to this therapy lies in increasing the persistence of T cells in the body.[23] For GEJ adenocarcinomas, trials are under way evaluating the efficacy of adoptive T-cell transfer.

Pancreatic cancers

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies worldwide with a fatality rate of 95%.[24] In a majority of the cases, early detection is rare, and patients usually present at locally advanced or metastatic stages, making effective treatment a remote possibility. About 60%–70% of pancreatic exocrine cancers arise from the head of the pancreas; 20%–25% arise from the body or tail; and the rest involve the whole organ.[25] The initial presentation depends on the location of the tumor; for example, tumors involving the head of the pancreas may present with jaundice, steatorrhea, and weight loss more often than tumors of the body and tail, but overall, the most common symptoms seen in exocrine pancreatic cancer are pain, jaundice, and weight loss.[26] PDAC has a very high fatality rate as there is a high resistance to treatment due to the immunosuppressive environment surrounding PDAC.[27]

ICIs in PDAC

Patients with PDAC were treated with anti-PD-1/PD-L1 (pembrolizumab and atezolizumab) and anti-CTLA-4 (ipilimumab) monotherapies, but these studies showed no substantial activity of checkpoint inhibitor monotherapy in unselected patients with advanced, pretreated, progressive PDAC.[28] However, PD-1 blockade appears to be efficient in a very small subgroup of patients with PDAC harboring a mismatch repair (MMR) deficiency, resulting in increased rates of somatic mutations potentially translating to neoantigens that can be recognized by the immune system. Hence, the FDA has approved the use of pembrolizumab in this subgroup of patients.[28]

Vaccine trials in PDAC

The two most promising vaccines so far in PDAC are GVAX (pancreatic cancer cell line that expresses granulocyte-macrophage colony stimulating factor (GM-CSF) and CRS-207 (live-attenuated *Listeria monocytogenes* strain that expresses mesothelin), which are commonly used together to induce T-cell immunity against pancreatic antigens such as mesothelin.[3] The interim results from the phase II ECLIPSE trial of a combination of GVAX and CRS-207 were promising, but the final results were negative.[29] However, the STELLAR trial, which is currently ongoing, evaluates the use of a combination of GVAX+CRS-207±nivolumab.

Indoleamine 2,3-dioxygenase (IDO) in PDAC

IDO metabolizes tryptophan, ultimately leading to the generation of nicotinamide adenine dinucleotide (NAD) and ATP and the depletion of tryptophan. Activation of this pathway leads to suppression of CTL via cell cycle arrest or anergy, and the activation of Tregs, which leads to the tumor escape mechanism. Indoximod is an oral IDO inhibitor under evaluation in clinical trials.[30] A phase II trial of indoximod plus gemcitabine/nab-pacitaxel showed promising antitumor activity for metastatic pancreatic cancers.[31]

CCR2 modulation in PDAC

The CCR2/CCL2 chemokine pathway plays a critical role in the recruitment of immunosuppressive macrophages/monocytes into the pancreatic cancer stroma. Pancreatic cancers secrete CCL2 to a large extent, thereby recruiting more monocytes into the pancreatic stroma.[3] Therefore, inhibition of the CCR2/CCL2 signaling pathway is predicted to improve innate antitumor immune responses by attenuating the immunosuppressive tumor microenvironment and improving survival.[32] The small molecule CCR2 inhibitor PF-04136309 is currently being studied with promising results and may lay the foundation for further investigation of the CCR2 pathway.[33]

Hepatobiliary cancers

Hepatocellular carcinoma (HCC) is usually seen in a background of chronic liver disease. Despite the availability of effective antiviral therapy, HCC continues to be on the rise due to the non-alcoholic fatty liver disease (NAFLD) pandemic and is the fourth leading cause of cancer death worldwide.[34] Hepatitis C virus-related and hepatitis B virus-related cirrhosis are associated with the highest incidences of HCC, but other etiologies with strong associations with HCC include NAFLD, alcohol-related liver disease and hereditary hemochromatosis.[35] Unfortunately, the diagnosis of HCC is often made when the patient has advanced disease or when there is some degree of liver impairment, thereby increasing the mortality associated with HCC. Patients with HCC may have a wide spectrum of clinical presentation. They may present with mild to moderate right upper quadrant abdominal pain, weight loss, early satiety or a palpable mass in the upper abdomen. Other presenting features may be that of the wide magnitude of paraneoplastic syndromes associated with HCC, or acute life-threatening conditions such as variceal bleeding. In patients with significant risk factors for HCC, screening is recommended through the use of

1. Radiological investigations: ultrasound, CT scan or MRI scan with contrast.
2. Laboratory investigations: alpha-fetoprotein (AFP).

The main aim of screening is early detection and treatment of HCC to prevent undesirable outcomes. Despite the availability of numerous therapeutic options, the current average 5 year survival rate in patients with HCC is only 43%.[36]

ICIs in HCC

The use of ICIs in clinical trials for the treatment of HCC have shown strong antitumor effect with an acceptable safety profile.[37] In 2007, FDA approved sorafenib for the treatment of advanced HCC as it increased the overall survival from 7.9 to 10.7 months.[38] A phase I/II study, the CheckMate 040 trial, first used nivolumab in patients who had progression of the HCC despite sorafenib treatment or those who exhibited intolerable toxicity, and promising results were published in 2017.[39] The phase III CheckMate 459 and CheckMate 9DX trials are ongoing to study the effectiveness of nivolumab in patients with HCC. Studies to determine the event-free survival, overall survival rates and the safety profiles for PD1 inhibitors (pembrolizumab), CTLA-4 inhibitors (tremelimumab and ipilimumab) and PD-L1 inhibitors (atezolizumab, avelumab, and durvalumab) are also ongoing.[40] However, the clinical trials combining ICIs with locoregional/targeted therapies might reveal potential future synergistic therapy for the treatment of HCC.[40]

Vaccine-based therapy in HCC

The two main cancer vaccine strategies include dendritic cells (DCs) and peptide vaccines. In preclinical mouse models, DC vaccines pulsed with tumor cell lysate effectively eradicated tumors; however, DC vaccines have demonstrated only marginal activity in patients with advanced HCC in humans.[41] Peptide vaccines use shared tumor-associated antigens (TAAs) such as AFP, glypican-3 (GPC3), and telomerase reverse transcriptase for HCC. Overall, TAA-based peptide vaccines have also had low clinical responses in the treatment of HCC.[41] However, literature does report the need for further clinical trials to examine a combination of DC or peptide vaccine-based therapy with other immunotherapies. The HEPAVAC project is currently studying a new cancer vaccine strategy using neoantigens, the products of non-synonymous tumor-specific mutations.[42]

ACT therapies in HCC

ACT is a promising approach currently being explored for HCC. The cell-based immunotherapy strategies being tried for the treatment of HCC include[41 43]

1. Cytokine-induced killer cells (CIKs): consist of a heterogenous mixture of immune cells generated ex vivo by expansion of mononuclear cells. They display strong cytolytic activity against tumor cells independent of MHC restriction. As per literature, CIK therapy prolongs recurrence-free survival and overall survival.
2. TCR-engineered T cells: T cells are generated by integrating cloned tumor antigen-specific TCR onto the T cells. In animal models, it has been demonstrated that TCR-engineered T cells that recognize AFP and GPC3 limit tumor growth significantly, whereas phase I clinical trials are under way, evaluating the use of AFP-specific TCRs and T-cell therapy targeting MAGEA1 for HCC in humans.
3. CAR-T: CAR-T helps eliminate tumor cells in in an MHC restriction-independent manner and hence also prevent the tumor escape mechanism through MHC downregulation. Clinical trials are currently exploring CAR-T therapy targeting AFP, MUC-1 and EpCAM for the treatment of HCC.

A deeper understanding of the immunology of HCC will allow for more specific targeted therapy in the near future.

Colorectal cancers

As per the American Cancer Society estimates in 2019, CRC was the second leading cause of cancer mortality with an estimated 8.3% of cancer-related death and 140 250 new cases of CRC diagnosed in 2018.[44] Over the past few decades, the mortality from CRC has been on the decline; however, the survival continues to remain poor for advanced disease. Literature reports that 86% of individuals diagnosed with CRC before the age of 50 years are symptomatic at the time of diagnosis, and this has strong associations with an advanced stage and poor survival outcomes.[45] Patients with

CRC can present with symptoms from the localized tumor such as hematochezia, melena, abdominal pain, change in bowel habits, features of bowel obstruction, abdominal distention, iron deficiency anemia of unknown origin, or symptoms due to the metastasis which tend to be organ specific. Presence of B-symptoms and lymphadenopathy are common. The diagnosis is established with colonoscopy and biopsy of the tumor with further histopathological evaluation of the specimen. Early detection and treatment of patients with CRC may improve overall survival.

ICIs in CRCs

The KEYNOTE 028 was a phase II clinical trial which studied the efficacy and side effect profile of pembrolizumab in patients with metastatic colon cancer with or without MMR deficiency.[46] Based on promising results from this trial in 2017, the FDA approved pembrolizumab for the treatment of advanced CRC with MSI-H or DNA mismatch repair (dMMR) malignancy that had progressed after conventional chemotherapy; however, additional studies are still warranted in this patient population. The CheckMate 142 was an open-label, multicenter, phase II clinical trial which enrolled patients with dMMR or mismatch repair-proficient (MMR-p) metastatic CRC to receive nivolumab either with ipilimumab or as monotherapy.[47] The immunotherapy showed significant benefits in patients with dMMR CRC with progression-free survival of 5.3 months, and 68% had achieved disease control for 12 weeks or longer.[47] Therefore, the FDA approved nivolumab for the treatment of MSI-H or dMMR metastatic CRC which had progressed following chemotherapy. The National Comprehensive Cancer Network clinical practice guidelines in Oncology V.4.2018 currently recognizes either nivolumab monotherapy, nivolumab+ipilimumab combination therapy, or pembrolizumab monotherapy as an acceptable standard of care treatment option for patients with dMMR or MSI-H mCRC tumors with progression after the standard first-line chemotherapy.[47] Multiple studies are currently under way, evaluating the use of anti-PD-1 agents for the treatment of metastatic CRC with microsatellite stability (MSS) or MMR-p, both in adjuvant and metastatic settings.

Vaccine-based therapy in CRCs

Different types of vaccines studied for CRC include autologous, peptide, and DC vaccines. Overall, cancer vaccines have not shown any survival benefits when compared with standard therapy or placebo for patients with CRC.[47] However, a combination therapy with talimogene laherparepvec local injection vaccine combined with systemic infusion of atezolizumab (PD-L1 blockade) is currently under evaluation for metastatic MSS CRC and may hold the key for the use of vaccine-based treatments in CRC.[47]

ACT therapies in CRCs

CAR-T therapy is currently in the early stages of clinical trials for the treatment of metastatic CRC. In animal models, T cells expressing the human GUCY2C-targeted chimeric antigen receptor have shown significant potential in eliminating metastatic CRC. As more receptors are being identified and T cell-specific delivery techniques are being improved, there may be substantial breakthroughs in the use of CAR-T for metastatic CRC.

Furthermore, like any therapy available, immunotherapeutic agents are associated with side effects. From a purely GI prospective, the side effects associated with immunotherapeutic agents, based on the class of the agent, include

1. ICIs: these agents are generally well tolerated, and the side effects tend to be mild and transient. The most common reported side effect with the use of ICI is watery, non-bloody diarrhea.[48] A specific subset of patients may develop colitis, which is characterized by fever, abdominal pain or mucous in the stools. Colitis secondary to the use of CTLA-4 agents is associated with mouth ulcers; anal lesions such as fistulas, abscesses or fissures; and other extraintestinal manifestations.[49] Literature also reports other manifestations such as asymptomatic elevations of liver enzymes, abdominal pain, nausea, vomiting, and hematochezia.[50] In rare cases with involvement of the upper GI tract, gastritis, esophagitis and aphthous ulcers may be seen.[51]
2. ACT therapy: infusions with this therapy are usually well tolerated by patients; however, some patients have reported mild infusion-related events.[52] Literature reports on-target adverse effects such as T-cell therapy for CRC leading to colitis or acute pulmonary, or T-cell therapy for esophageal cancer leading to seizures or coma.[53] Although, these adverse effects are not life-threatening, they may limit the treatment strategy. Additionally, ACT may lead to cytokine syndrome, which is characterized by large-scale activation of T cells on recognition of the malignant cells and can present with symptoms such as fevers, rigors, hypotension and hypoxia.[53] However, the main concern of T-cell therapy is the potential for delayed, on-target but off-tumor adverse effects, which are currently unknown and may be life-threatening.
3. Vaccine-based therapy: cancer vaccines have reported minimal toxicities in most of the clinical trials conducted thus far. However, additional large population-based clinical trials are needed to identify associated complications and adverse effects.

Over the past decade, our knowledge about the relationship between various cancers and the immune system has taken significant leaps forward and continues to evolve. Although significant advances have been made in the field, challenges still exist. In this review of literature, we have briefly outlined the mechanism of actions of different agents, their approval by the FDA and use for different cancers. However, the decision to select an agent for a particular type and stage of cancer, and the results for each clinical trial, although interesting, are outside the scope of this review. Additional information on the specific agent and the specific result can be obtained online (https://clinicaltrials.gov/).[54]

CONCLUSION

GI cancers consist of esophageal, gastric, pancreas, hepatobiliary and CRCs which are some of the major causes of mortality worldwide and in the USA. Immunotherapy, which is focused around developing agents to stimulate or suppress the immune system to fight off a wide spectrum of diseases, particularly cancers, may be an immense

breakthrough in modern-day medicine and the future of cancer treatment. Immunotherapeutic agents are of interest to scientists because of their specificity against TAAs. The main subtypes of immunotherapeutic currently being evaluated through clinical trials in detail include ICIs, adoptive T-cell therapy and vaccine-based therapies. The US FDA has approved multiple immunotherapy agents for the treatment of GI malignancies; however, their use has mainly been limited to either advanced stage of the malignancy or treatment refractory cancers. For the treatment of GI malignancies, combination therapy consisting a combination of either immunotherapy agents with different mechanisms of action or an immunotherapy agent with other treatment modalities may hold the key for better overall survival outcomes and may become the treatment of choice moving forward. However, additional studies are needed to determine the exact efficacy of the numerous immunotherapeutic agents available. Clinical trials evaluating the use of combination therapies are ongoing.

Contributors All authors have contributed to the manuscript and agreed with the final version of the manuscript. The final authorship contribution statement is as follows: DSD and AK are credited with substantial contribution to the design of the work, literature review of all the sections discussed, the revision of critically important intellectual content, final approval of the published version, and agreement of accountability for all aspects of the work. JS and MA are credited with significant design of the tables and graphs, literature review of all sections, revision of important intellectual content for the discussion, and agreement of accountability for all parts of the work. ML is credited with literature review, final content write-up and agreement of accountability for all aspects of the work.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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