Immunotherapy in Gastrointestinal Malignancies

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Abstract

Gastrointestinal (GI) cancers represent a variety of malignancies, each with a unique interplay between the tumor and local immune microenvironment. The successes that immunotherapy, particularly immune checkpoint inhibition, has brought to various other solid tumors have largely not yielded the same benefits to patients with GI cancers. There are subsets of patients for whom immunotherapy has been FDA approved in recent years. For example, anti-PD-1 therapy is approved for patients with pretreated hepatocellular carcinoma. Additionally, patients with PD-L1-positive gastric cancer are eligible to receive anti-PD-1 therapy in the third line setting. Outside of the rare subset of patients who harbor MSI-H/dMMR tumors, the vast majority of patients with colorectal, anal, biliary tract, and pancreatic cancers have not responded to single-agent immune checkpoint inhibitors. Innovative techniques with thoughtful treatment combinations, adoptive cell therapy, CAR-T cells, as well as novel predictive biomarkers are needed to bring the benefits of immunotherapy to the majority of patients with GI malignancies.

Keywords

Immunotherapy · Immune checkpoint inhibitor · Colorectal cancer · Gastric cancer · Pancreatic cancer · Biliary tract cancer · Hepatocellular carcinoma · Anal cancer · Cancer vaccine · Adoptive cell therapy · CAR-T cells

Introduction

In 2019, over 300,000 individuals in the United States are expected to be diagnosed with a gastrointestinal (GI) cancer, and roughly 50% of that number are expected to die from a GI malignancy [1]. GI cancers represent a wide variety of diseases with distinct histopathologies, oncogenic drivers, and mechanisms of treatment resistance. In order to assess the current role of immunotherapy in GI cancers, one must consider each primary site individually. As a point of illustration, antibodies targeting PD-1 and/or CTLA-4 appear in the National Comprehensive Cancer Network guidelines for the treatment in particular cases of

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gastric, colorectal, and primary hepatic cancers, but they do not currently play a role in the standard of care treatment of virtually any patients with pancreatic cancer [2–5]. There are numerous hypotheses for the variability in response to immunotherapy by disease type in GI cancers. Among these explanations are differences in tumor mutational burden and variation in the presence and makeup of tumor-infiltrating lymphocytes [6–8].

The most significant development in the treatment of GI malignancies with immunotherapy occurred in May 2017 when the United States Food and Drug Administration (FDA) approved the PD-1 monoclonal antibody, pembrolizumab, for any pretreated unresectable solid tumor with microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR) [9]. This approval was based on the results of five early-phase single-arm trials with demonstration of a 39.6% objective response rate and 7.4% complete response rate across all solid tumors in this patient population. Ninety of the 149 patients with MSI-H or dMMR had colorectal cancer with a response rate of 36% in this patient group.

Below, we will assess the state of immunotherapy in GI cancers according to each disease site. We will evaluate the successes and failures and comment on future strategies being utilized to combat resistance to immunotherapy.

Gastroesophageal Cancer

Current Evidence

The expression of programmed death ligand 1 (PD-L1) in gastric cancer had been well established prior to the widespread use of checkpoint inhibitors in clinical practice [10, 11]. Sun et al. described in 2006 the association between PD-L1 expression by immunohistochemistry (IHC) in gastric cancer and poor clinical prognosis, with PD-L1 expressing tumors exhibiting higher rates of lymph node metastasis, larger tumor size, greater depth of invasion and decreased survival. In 2016, the results of the phase 1b KEYNOTE-012 study were published, demonstrating the tolerability and promising efficacy of pembrolizumab in the treatment of 39 patients with recurrent or metastatic PD-L1-positive gastric or gastroesophageal junction (GEJ) cancer [12]. The overall response rate (RR) was 22% and median overall survival (OS) was 11.4 months. The phase 2 KEYNOTE-059 study enrolled 259 patients with previously treated gastric and GEJ cancers, including both PD-L1-positive and -negative tumors [13]. The reported objective RR was 11.6% when including all patients, but was higher at 15.5% in the PD-L1-positive cohort, compared with 6.4% in the PD-L1-negative cohort. Complete responses were seen in patients with both PD-L1-positive and PD-L1-negative tumors. Based on the results of the KEYNOTE-059 study, the FDA granted accelerated approval to pembrolizumab for patients with PD-L1-positive recurrent or metastatic gastric or GEJ cancers. In the phase 3 KEYNOTE-061 trial, 592 patients with gastric or GEJ cancers who had progressed on first-line platinum + fluoropyrimidine chemotherapy were randomized to second-line pembrolizumab or paclitaxel [14]. The initial 489 patients were enrolled regardless of PD-L1 status, but the remaining patients were required to have a combined positive score (CPS) of at least 1, after a protocol amendment. The median OS in the pembrolizumab group was 9.1 months compared to 8.3 months in the paclitaxel group, (hazard ratio [HR] 0.82, one-sided $P = 0.04$). The study authors concluded that pembrolizumab did not significantly improve OS compared with paclitaxel for this population receiving treatment in the second-line. They also noted that protocol-specific and post-hoc subgroup analyses did suggest better efficacy of pembrolizumab in patients with higher levels of PD-L1 expression.

The role of other immune checkpoint inhibitors in patients with gastric or GEJ cancers was assessed in the ATTRACTION-2 trial, performed in East Asia and the CheckMate-032 trial, which studied a Western population [15, 16]. The ATTRACTION-2 trial randomized 493 patients with gastric or GEJ cancers who had received at least two prior lines of systemic therapy to the PD-1 monoclonal antibody, nivolumab or placebo, in a 2:1 ratio. The median OS in the nivolumab group was 5.26 months, compared to 4.14 months in the placebo group (HR 0.63,

P lt; 0.0001). Ten percent of the patients in the nivolumab group experienced grade 3 or 4 toxicity compared with 4% of the placebo group. The phase 1/2 CheckMate-032 trial randomized 160 patients with pretreated metastatic esophageal, gastric, and GEJ cancers to nivolumab alone, nivolumab 1 mg/kg + the CTLA-4 monoclonal antibody, ipilimumab 3 mg/kg or nivolumab 3 mg/kg + ipilimumab 1 mg/kg. Objective RR in each group was 12%, 24%, and 8%, respectively, with 12-month OS rates of 39%, 35%, and 24%.

The PD-L1 antibody, avelumab, has been studied in advanced gastric and GEJ cancers as well. A group of 150 patients with gastric or GEJ cancers were enrolled in the phase 1b JAVELIN Solid Tumor trial, 90 in the first-line maintenance setting and 60 in the second-line [17]. In both groups, the RR was 6.7%. Median PFS in the first-line maintenance group was 2.8 months, compared with 1.4 months in the second-line group. The JAVELIN Gastric 100 study is an ongoing phase III trial that has enrolled patients with advanced gastric and GEJ cancers who have at least stable disease following 12 weeks of first-line oxaliplatin/fluoropyrimidine chemotherapy with randomization to continuation of chemotherapy or avelumab maintenance [18]. The phase III JAVELIN Gastric 300 trial randomized 371 patients with advanced gastric or GEJ cancers to either avelumab or physician's choice chemotherapy in the third-line setting [19]. Median OSs, the primary endpoint, in the avelumab and chemotherapy arms were 4.6 and 5.0 months (HR 1.1, $P = 0.81$), respectively. Median PFS was also shorter in the avelumab arm (HR 1.73, $P > 0.99$).

Future Strategies

Early results using immunotherapy in gastroesophageal cancers have revealed that the majority of patients in the unselected population do not respond to monotherapy with checkpoint inhibitors. Adoptive cell therapy and vaccines have been similarly disappointing in their clinical efficacy. There do, however, appear to be a population of patients who do benefit from immunotherapy, beyond the MSI-H and dMMR patients. Teasing out what are the common characteristics of these patients is the challenge for the next wave of clinical trials with immunotherapy.

Among these populations being studied are patients with a high tumor mutational burden (TMB) and patients with HER-2 amplified tumors. One study being conducted in Japan is a basket study of multiple GI cancers using nivolumab monotherapy for patients with high TMB, as measured by the circulating tumor DNA Guardant360® panel [20]. At the 2019 GI Cancer Symposium, results from a phase II study of 24 patients with HER-2 amplified gastroesophageal cancers treated with pembrolizumab, trastuzumab, and chemotherapy in the first-line setting demonstrated an RR of 83% with three complete responses and a median PFS of 11.4 months [21]. This combination is currently being evaluated further in the phase III KEYNOTE 811 trial [22]. Another study in Japan is evaluating the combination of nivolumab and trastuzumab combined with chemotherapy in patients with HER-2 amplified gastric cancers [23].

One effort to maximize the efficacy of immunotherapy in gastroesophageal malignancies is to optimize the timing of treatment with checkpoint inhibitors. Moving immunotherapy to earlier lines of systemic therapy is one area of focus. Results of the phase III JAVELIN Gastric 100 study are eagerly awaited, in which avelumab is being evaluated as a maintenance therapy in the first-line setting [18]. The phase III KEYNOTE 181 study randomized patients with advanced esophageal or GEJ cancers to pembrolizumab or physician's choice in the second-line setting. While there was no difference in OS in the intention to treat population, patients with a CPS ≥ 10 treated with pembrolizumab were found to have a median OS of 9.3 compared to 6.7 with chemotherapy (HR 0.69, $P = 0.0074$) [24]. Another strategy being assessed in ongoing clinical trials involves the use of checkpoint inhibitors in earlier stages of disease. For example, the combination of perioperative avelumab in combination with chemoradiation in stage II/III esophageal cancer is being studied [25] (Table 5.1).

Table 5.1 Selected active clinical trials with immune checkpoint inhibitors in gastroesophageal cancers

Agent(s)	Patients	Phase	Clinical trial identifier	Notes
SHR1210 (PD-1) ± apatinib ± S1	Neoadjuvant for resectable gastric cancer	II	NCT03878472	Not yet recruiting; China
Multiple combinations: atezolizumab ± chemotherapy ± targeted therapy	Unresectable or metastatic gastric or GEJ cancer	Ib/II	NCT03281369	Recruiting; International – including US
Multiple combinations involving nivolumab and relatlimib (LAG-3)	Advanced gastric or GEJ cancers – first line	II	NCT03662659	Recruiting; International – including US
Nivolumab + ipilimumab + chemoradiation	Perioperative for resectable gastric cancer	I/II	NCT03776487	Recruiting; US
Margetuximab (HER2) + Pembrolizumab	Advanced HER2+ gastric or GEJ cancer	I/II	NCT02689284	Active, not recruiting; International – including US
Pembrolizumab + TS-1 + cisplatin/oxaliplatin	Advanced gastric cancer – first line	IIb	NCT03382600	Recruiting; Japan

Colorectal Cancer

Current Evidence

The subset of patients with colorectal cancer (CRC) who have benefited most from advances in immunotherapy have been those whose tumors are MSI-H or harbor dMMR. MSI-H CRC represents the minority of CRC cases, less than 20%, when all stages are included, though they are associated with a better prognosis compared with microsatellite stable (MSS) CRC, particularly in early-stage disease [26, 27]. Of patients with metastatic CRC, only 4–5% are MSI-H, and the majority of these cases result from sporadic mutations in mismatch repair proteins, rather than being associated with Lynch Syndrome [28]. The immunogenicity of MSI-H tumors has been well-described, with the primary hypothesis being that their high mutational load leads to a higher density of tumor-infiltrating lymphocytes (TIL) and increased expression of checkpoint receptors [29–31].

MSI-H status has subsequently proven to be a powerful predictive biomarker for response to immune checkpoint inhibitors. This was initially demonstrated with the use of pembrolizumab in the phase II KEYNOTE-016 study, which included a cohort of patients with pretreated metastatic dMMR and mismatch repair-proficient CRC [32]. Pembrolizumab significantly increased median PFS (HR 0.10, $P < 0.001$) and median OS (HR 0.22, $P = 0.05$) in the dMMR cohort compared with the mismatch repair-proficient cohort. The KEYNOTE-164 study evaluated pembrolizumab in MSI-H CRC after at least two lines of therapy (cohort A) and at least one line of therapy (cohort B). In cohort A, the RR was 27.9%, and in cohort B the RR was 32% with two complete responses and a 12-month OS rate of 76% [33, 34]. The results of these and other early-phase studies using pembrolizumab in pretreated patients with solid tumors and dMMR led to the 2017 FDA primary site-agnostic approval of pembrolizumab in this setting [9].

The CheckMate 142 study was a phase II clinical trial assessing nivolumab monotherapy or nivolumab in combination with ipilimumab in patients with MSI-H and MSS metastatic CRC [35]. The results from the initial 74 patients with MSI-H metastatic CRC treated with nivolumab monotherapy were published in 2017. The objective RR was 31.1%, all of which were partial responses, and the median duration of response was not reached at the time of publication. Median PFS was 14.3 months, 12 month OS was

73%, and median OS was not reached. The results from the combination nivolumab plus ipilimumab arm were reported in 2018 [36]. There were 119 patients who received combination therapy with an objective RR of 54.6%, including 3.4% with complete responses. Impressively, 83% of responding patients had responses that lasted at least 6 months, with a median duration of response that was not reached. Neither median PFS nor OS were reached in this group, though 12 month PFS and OS were 71% and 85%, respectively. The rate of grade 3–4 treatment-related adverse events (TRAEs) was higher in the combination arm (32%) compared with nivolumab monotherapy (20%), but the rates of any-grade TRAEs were similar (73% vs 70%). Based on the results of the CheckMate 142 study, the FDA granted accelerated approval to nivolumab and combination nivolumab plus ipilimumab for patients with MSI-H or dMMR metastatic CRC [37, 38].

Results from the Canadian Cancer Trials Group (CCTG) CO.26 study were presented at the 2019 Gastrointestinal Cancers Symposium [39]. This phase II trial randomized patients with refractory metastatic CRC 2:1 to the combination of the anti-PD-L1 antibody, durvalumab, plus the anti-CTLA-4 antibody, tremelimumab, or best supportive care. None of the 180 patients enrolled were known to have MSI-H tumors. There was no difference in median PFS between the arms (1.8 vs. 1.9 months), but there was a trend towards increased OS with a median OS of 6.6 months in the treatment arm and 4.1 months in the best supportive care arm (HR 0.72, $P = 0.07$).

Future Strategies

With the promising results of many phase II clinical trials in metastatic CRC, particularly in the MSI-H/dMMR space, a number of phase III have been initiated to confirm the benefits of immunotherapy in this malignancy. Most of these studies are evaluating checkpoint inhibitors in patients with metastatic CRC. KEYNOTE 177 is evaluating MSI-H metastatic CRC patients treated with pembrolizumab compared with standard chemotherapy in the first-line setting [40]. The COMMIT Trial is evaluating the PD-L1 inhibitor, atezolizumab, in a three-arm study in MSI-H metastatic CRC patients in the first-line setting: atezolizumab monotherapy vs. FOLFOX plus atezolizumab plus bevacizumab vs. FOLFOX plus bevacizumab [41]. The strategy of employing immunotherapy in the first-line setting rather than in refractory patients was also evaluated in a cohort of patients in the CheckMate 142 study. Results from this group which evaluated nivolumab plus ipilimumab in MSI-H/dMMR patients with treatment-naive metastatic CRC were presented at the European Society for Medical Oncology (ESMO) 2018 Congress [42]. Forty-five patients received combination checkpoint inhibition with an overall RR of 60%. PFS and OS at 12 months were 77% and 83%, respectively. The results of these studies may significantly alter the current standard of care for front-line therapy in patients with MSI-H metastatic CRC.

Another avenue of exploration in patients with MSI-H CRC is in treatment of these patients with stage III disease. Two ongoing studies evaluating adjuvant checkpoint inhibitors are the ATOMIC and POLEM trials [43, 44]. The ATOMIC trial is evaluating adjuvant FOLFOX with or without atezolizumab. The POLEM trial is evaluating maintenance avelumab for 24 weeks after completion of adjuvant chemotherapy and includes patients with POLE exonuclease domain mutations.

Despite the successes of several checkpoint inhibitors in the treatment of patients with MSI-H metastatic CRC, the vast majority of patients with metastatic CRC have not realized any benefit from treatment with these agents. Strategies aimed at turning these immunologically "cold" cancers into inflamed tumors are desperately being sought. Several ongoing clinical trials combining radiation therapy with immunotherapy are aiming to harness the potential of the "abscopal effect" in treating MSS CRC [45–47]. In this hypothesis, radiation therapy would have a local effect of cell death and surge in inflammatory cytokines. Downstream effects of the cytokine storm include upregulation of tumor

Table 5.2 Selected active clinical trials with immune checkpoint inhibitors in colorectal cancers

Agent(s)	Patients	Phase	Clinical trial identifier	Notes
Avelumab + Cetuximab + Irinotecan	Refractory metastatic MSS CRC	II	NCT03608046	Recruiting; Belgium
Avelumab + chemotherapy	Stage 3 MSI-H or POLE mutant CRC – adjuvant therapy	III	NCT03827044	Recruiting; UK
Chemotherapy ± atezolizumab	Stage 3 dMMR CRC – adjuvant therapy	III	NCT02912559	Recruiting; US
Cabozantinib + atezolizumab	Multiple advanced solid tumors including CRC	Ib/II	NCT03170960	Recruiting; International – including US
Multiple combinations including atezolizumab ± selicrelumab (CD40) ± targeted therapy	Metastatic CRC	Ib/II	NCT03555149	Recruiting; International – including US
FOLFOX + bevacizumab ± nivolumab	Metastatic CRC – First line	II/III	NCT03414983	Recruiting; International – including US
FOLFOX + bevacizumab ± atezolizumab and atezolizumab alone	Metastatic dMMR CRC	III	NCT02997228	Recruiting; US
Nivolumab + Trametinib ± ipilimumab	Refractory metastatic CRC	I/II	NCT03377361	Recruiting; International – including US
Tremelimumab + durvalumab	Metastatic CRC to liver prior to metastasectomy	I	NCT02754856	Recruiting; US
Nivolumab + Relatlimab (LAG-3)	Advanced MSS CRC	II	NCT03642067	Recruiting; US

neoantigen expression and priming of the immune microenvironment, eventually leading to off-target effects of immune activation on other sites of disease. The addition of immune checkpoint inhibitors to cytotoxic chemotherapy, such as FOLFOX, has also been proposed as a mechanism by which to promote an immune response to CRC [48, 49]. Combining immune checkpoint inhibitors with therapies targeting MEK or VEGF has also been studied as a strategy to expand the benefits of immunotherapy to MSS CRC patients with preliminary results indicating some responses in this groups of patients [50, 51]. However, the phase III study, IMblaze370, reported in 2019 that it did not meet its primary endpoint of improved OS with third-line combination atezolizumab and MEK inhibitor, cobimetinib, compared with regorafenib in an almost entirely MSS population [52]. It is clear from these results that significant hurdles still remain in bringing the efficacy of immunotherapy to the majority of patients with CRC (Table 5.2).

Anal Cancer

Current Evidence

Squamous cell carcinoma (SCC) of the anus is a less common malignancy of the GI tract. The pathophysiology of anal cancer resembles other mucosal malignancies caused by the human papillomavirus (HPV), as this infectious agent is associated with the vast majority of cases of anal SCC [53–55]. The safety and efficacy of pembrolizumab was evaluated in the phase Ib multicohort study, KEYNOTE 028 [56]. One cohort of this study included 24 patients with PD-L1-

positive advanced anal SCC. The overall RR was 17% and disease control rate was 58%. 64% of patients experienced TRAEs. The multi-center phase 2 trial, NCI9673, evaluated the clinical benefit of single-agent nivolumab in patients with pretreated metastatic anal SCC [57]. 37 patients received treatment with an RR of 24%, including two complete responses. Immunohistochemistry analysis of tumor samples from patients in this study demonstrated a significantly higher concentration of PD-1 and PD-L1 expression in tumors of those who responded to nivolumab compared with those that did not respond. Authors from both of these studies concluded that given the lack of standard of care treatment for patients with advanced disease, checkpoint inhibitors warrant further investigation as a novel therapeutic option for patients with SCC of the anus.

Future Strategies

Similar to other cancers in which early-phase studies identified evidence of clinical benefit of single-agent PD-1/PD-L1 inhibition, the addition of an anti-CTLA-4 antibody has been proposed to increase clinical activity. An amendment to the NCI9673 study added an additional arm to the phase II study, which will evaluate the combination of nivolumab and ipilimumab in patients with refractory metastatic SCC of the anus [58]. This portion of the study is expected to be completed in early 2020. Pembrolizumab is also being studied as monotherapy in a phase II study in refractory patients with metastatic anal SCC [59]. A phase II study in France will be assessing the efficacy of the combination of atezolizumab and an HPV-directed vaccine, UCPVax, in patients with HPV positive cancers [60]. In an effort to move immunotherapy into earlier stages of anal cancer, a randomized phase II study is evaluating the addition of maintenance nivolumab after combined modality therapy compared to observation for patients with high-risk stage II-IIIB SCC of the anus [61].

Hepatobiliary Cancer

Current Evidence

Hepatocellular Carcinoma

In terms of access to treatment, patients with advanced hepatocellular carcinoma (HCC) have benefited more than any other GI malignancy from the development of immune checkpoint inhibitors. The liver maintains a crucial role in the body's complex system of immune regulation and becomes disrupted during heightened inflammatory states from pre-HCC liver conditions such as chronic hepatitis B and C infections.

Tremelimumab was the first immune checkpoint inhibitor studied in HCC [62]. Of the 20 patients in the initial clinical trial who received treatment, 17 were assessable for response, of whom 17.6% had a partial response. All of these patients had chronic hepatitis C virus infection, and the tolerance of the anti-CTLA-4 antibody was fairly good. In 2017, single-agent nivolumab was granted accelerated approval by the FDA as a second-line agent without any biomarker requirement [63]. This approval was based on the CheckMate 040 study, a phase I/II trial which included 262 total patients, some in the first-line and some having had been previously treated with sorafenib [64]. The safety profile was manageable in this study, and the objective RR was 20% (95% Confidence Interval, 15–26) with nivolumab 3 mg/kg in the dose-expansion phase. The phase II KEYNOTE 224 trial evaluated pembrolizumab in patients with HCC previously treated with sorafenib. Of the 104 patients treated, 18 (17%) experienced a response, with one complete response. OS was 54% at 12 months. Based on the results of KEYNOTE 224, pembrolizumab carries a category 2B recommendation from the NCCN in patients with pretreated HCC [4].

Biliary Tract Cancers

Biliary tract cancers (BTCs) are a rare subset of GI malignancies, comprising cholangiocarcinoma and gall bladder carcinoma. Clinical trials assessing the efficacy of immune checkpoint

inhibitors in patients with BTCs have been largely disappointing. As is the case across the spectrum of solid tumors, the group of patients who have seen clinical benefit are the small population of BTC patients who have tumors with MSI-H or dMMR, a percentage reported as low as 1% and as high as 10% [65, 66]. The phase II KEYNOTE-158 trial was a basket trial that assessed the response to pembrolizumab among several advanced solid tumors. A total of 104 patients with BTC were included, none of whom had MSI-H tumors [67]. The overall RR was 5.8%, with 17 patients (16%) achieving a best response of stable disease. The median PFS was 2.0 months, and the median OS was 9.1 months.

Future Strategies

Novel treatment strategies with immunotherapy in HCC are primarily aiming to introduce immune checkpoint inhibitors in earlier lines of therapy. There is sound biological rationale in this approach, as the immunosuppressive nature of the HCC tumor microenvironment tends to become more pronounced as the disease progresses [68]. The phase III CheckMate 459 study is a randomized control trial comparing first-line sorafenib and nivolumab in patients with advanced HCC [69]. Another intriguing strategy being explored is the combination of oral tyrosine kinase therapy with immune checkpoint inhibitors. For example, two expansion arms have been opened in the CheckMate 040 study which will analyze the effect of cabozantinib plus nivolumab with or without ipilimumab [70]. Whether the potential benefits of increased response to these combinations will outweigh the likely worsened toxicity profile is uncertain.

For patients with BTCs, the role of immunotherapy in the treatment of advanced disease is uncertain. The available evidence thus far suggests that single-agent checkpoint inhibitors will not provide any benefit to BTC patients outside of the minority with MSI-H/dMMR tumors. Other immune targets such as T-cell immunoglobulin and mucin-domain containing 3 (TIM3), lymphocyte activation gene (LAG3), and indoleamine 2,3-dioxygenase (IDO) are currently being studied in various combinations [71]. Outside of immune checkpoint inhibitors, other immunotherapy strategies that have been evaluated in BTCs include vaccines and adoptive cell therapy. Two antigens that are expressed on >80% of BTCs include mucin protein 1 (MUC1) and Wilm's tumor protein 1 (WT1) [71]. In a phase I study of eight BTC patients with gemcitabine and a WT1 vaccine, half of the patients achieved stable disease at 2 months [72]. Another phase I study with a MUC1 vaccine in eight BTC and pancreatic cancer patients yielded an even lower disease control rate [73]. A clinical trial assessing adjuvant adoptive T-cell therapy combined with a postoperative dendritic cell vaccine in resectable intrahepatic cholangiocarcinoma patients, increases in median PFS and OS were seen from 7.7 to 18.3 months and 17.4 to 31.9 months, respectively, when compared to surgery alone [74]. Patients with BTCs will be included in a phase I pilot trial at the University of Texas MD Anderson Cancer Center that evaluates CD8+ T-cell therapy with pembrolizumab in a variety of advanced GI malignancies [75].

Pancreatic Cancer

Current Evidence

Pancreatic ductal adenocarcinoma (PDAC) in many ways represents the quintessential immunologically "cold" tumor. The microenvironment of PDAC tumors is characterized by a low density of CD8+ T-cells, disrupted expression of major histocompatibility complexes (MHC), and immunosuppressive enzymes and cytokines [76, 77]. Several studies have concluded that PD-L1 expression in PDAC is associated with a poor prognosis [78]. In the face of these obstacles, several clinical trials have evaluated the efficacy of immune checkpoint inhibitors in patients with advanced PDAC.

There were 14 patients with PDAC who received single-agent nivolumab in the landmark phase I trial whose results were published in 2012 [79]. However, none of the PDAC patients

achieved an objective response. One patient with PDAC was included in a phase I study of pembrolizumab as a single agent and failed to show a response to treatment [80]. Ipilimumab as a monotherapy at a 3 mg/kg dose was evaluated in a phase II trial for patients with advanced PDAC [81]. None of the 27 patients included in the study achieved an objective response, though one patient continued ipilimumab beyond initial progression and achieved a significant delayed response. In a study at Johns Hopkins, ipilimumab was combined with the GM-CSF cell-based vaccine, GVAX in patients with advanced PDAC. Compared to ipilimumab alone, the combination of ipilimumab and GVAX demonstrated trends towards increased median OS (3.6 vs. 5.7 months, HR 0.51, $P = 0.07$) and 1 year OS (7% vs 27%) [82].

The combination of chemotherapy and immunotherapy was assessed in a phase Ib/II study that evaluated the combination of gemcitabine, nab-paclitaxel, and pembrolizumab in patients with metastatic PDAC [83]. Seventeen patients were treated, with 11 evaluable in the treatment-naïve phase II component. The authors reported three patients with a partial response, with one as long as 15 months, and a disease control rate of 100%. For treatment-naïve patients, median PFS and OS were 9.1 and 15.0 months, respectively.

Single-agent immune checkpoint inhibition is currently only a viable treatment option for patients with MSI-H/dMMR PDAC, a population that may represent as little as <1% of all PDAC patients [84, 85].

Future Strategies

Similar to other cancer types, interest has been shown in the combination of radiation therapy immune checkpoint inhibitors. Results from a recent clinical trial were presented at the 2019 Gastrointestinal Cancers Symposium which include 51 patients with advanced PDAC who were treated with a combination of stereotactic body radiation therapy (SBRT) and durvalumab with or without tremelimumab. The authors reported an overall RR of 9.6%, with two patients having achieved partial responses lasting greater than 12 months. Results from a phase I trial combining hypofractionated radiotherapy with pembrolizumab were recently published [86]. Four patients with advanced PDAC were included, and none of the four demonstrated an objective response by RECIST criteria. A number of other studies are currently ongoing, which include the combination of radiation therapy and immunotherapy in patients with PDAC [87–89].

The targeting of CD40 with an agonist has been demonstrated to reverse immune suppression in PDAC murine models by way of macrophage activation, and combination of a CD40 agonist with gemcitabine led to tumor regression in human PDAC tumors [90]. At the American Association for Cancer Research (AACR) 2019 Annual Meeting, an interim analysis of a phase Ib study was presented that combined gemcitabine, nab-paclitaxel, the CD40 agonist, APX005M with or without nivolumab in patients with treatment-naïve metastatic PDAC [91]. Of the 24 patients with evaluable disease, 20 experienced a reduction in tumor size. Thirteen patients discontinued therapy due to an adverse event. These preliminary results have led to the initiation of a randomized phase II study with these agents.

Adoptive cell therapy and chimeric antigen receptor T-cell (CAR-T) therapy are additional approaches that have gained momentum for future evaluation in PDAC patients. Adoptive transfer of MUC1-specific T-cells has been studied in PDAC mouse models with evidence of anti-tumor effect [92]. An ongoing study at the National Cancer Institute is evaluating adoptive T-cell therapy in a variety of metastatic solid tumors [93]. CAR-T cells have significantly advanced the treatment options of certain patients with relapsed and refractory hematologic malignancies. Attempts to carry these benefits over to patients with solid tumors are in their beginning stages. For patients with PDAC in particular, various CAR-T cells have been engineered to recognize MUC1, carcinoembryonic antigen (CEA), and mesothelin (MSLN) in mouse models [94–96]. There is cautious optimism that CAR-T cell therapy for PDAC may represent a novel immunotherapeutic strat-

egy that could be applicable to a broader population of patients than those who currently benefit from immune checkpoint inhibitors.

Conclusion

The age of immunotherapy is in full effect throughout the field of oncology. The excellent tolerability, high response rates, and, most significantly, durable responses, seen in patients treated initially with checkpoint inhibitors in the field of melanoma, have now been expanded to many patients with lung, urothelial, and kidney cancers, among other solid tumor types. GI malignancies have by and large been noticeably absent from those who have realized the benefits of immunotherapy outside of a few groups of patients. Among these patients who have received FDA approval for treatment with immune checkpoint inhibitors are patients with gastric and GEJ cancers whose tumors are positive for PD-L1 and patients with HCC who have previously received sorafenib. Response rates in these populations remain relatively low, but those who do respond still have the potential to achieve durable clinical benefit. Further research into other predictive biomarkers is being conducted and represents a desperate need in the field of immunotherapy.

For the majority of patients with GI malignancies, including almost all patients with pancreatic, biliary tract, and colorectal cancers, new strategies are needed beyond single-agent checkpoint inhibitors if immunotherapy is going to make its way into the clinic. Novel combination strategies with chemotherapy, radiotherapy, or targeted therapy that are currently being studied may provide an additional immunologic boost that some of these tumors need to overcome resistance to immunotherapy. The next generation of cancer vaccines, adoptive cell therapy, and CAR-T cells for GI malignancies represent additional avenues that may be able to harness the promise of immunotherapy. As each year passes, the knowledge and understanding of susceptibilities and resistance mechanisms of GI cancers to current immune therapies will continue to grow. Optimism remains that at some point the era of immunotherapy will reach the majority of patients with GI cancers, though when and in what form remains to be seen.

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