Review Article

Immunotherapy and radiation therapy for gastrointestinal malignancies: hope or hype?

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Abstract: Immunotherapy represents the newest pillar in cancer care. Although there are increasing data showing the efficacy of immunotherapy there is a spectrum of response across unselected populations of cancer patients. In fact, response rates can be poor even among patients with immunogenic tumors for reasons that remain poorly understood. A promising clinical strategy to improve outcomes, which is supported by an abundance of preclinical data, is combining immunotherapy with radiation therapy. Here we review the existing evidence and future directions for combining immunotherapy and radiation therapy for patients with gastrointestinal cancers.

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Introduction

Classical radiobiology has focused primarily on intracellular effects from radiation therapy (RT) and DNA damage mediated cell death (1). However, more contemporary data suggest that the cytotoxic effects of RT are intimately related and dependent on the immune system. In 2009 researchers from University of Chicago demonstrated the importance of CD8+ T cells for the therapeutic effects from ablative RT (2). This finding was replicated by a group from Japan (3), and demonstrated that CD8+ T cell depletion could induce radioresistance.

Immune mediated effects of RT begin with the expression of damage-associated molecular patterns (DAMPs) (4). These factors include the release of high mobility group box 1 (HMGB1) nuclear protein by dying tumor cells, which interact with Toll-like receptor 4 (TLR4) on dendritic cells (DCs) (5). HMGB1 may be expressed even when cell viability is unaltered with RT (6), and results in dose-dependent immunostimulation in the local microenvironment. In a rodent melanoma model, DCs exhibited increased major histocompatibility complex (MHC) expression within 48 hours of RT exposure (2). This permits the presentation of normally suppressed tumor associated antigens that are required for immune mediated cell kill.

RT has stimulatory, but also inhibitory effects on the immune system. High dose RT may also increase PD-L1 expression and terminate the inflammatory response through negative feedback. As a result, anti-cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) and anti-programmed death-1 (PD-1) inhibitors may work synergistically to improve outcomes after RT (7,8). In a murine hepatocellular carcinoma (HCC) model, RT was found to upregulate PD-L1 expression through an IFN-γ/STAT3 mediated signaling pathway. As a result, the

combination of anti-PD-L1 treatment with RT induced tumor growth delay and improved survival in this cancer model (9).

Radiotherapy has been shown to generate abscopal effects resulting in the response of metastatic tumor deposits not directly treated with RT. Excitement regarding the clinical utility of this phenomena was fueled by a melanoma study examining the use of RT following ipilimumab. Roughly half of all patients in this study experienced an abscopal response with a corresponding increase in survival from 8.3 to 22.4 months (10). Although the mechanism of these effects is not clear, an increase in tumor infiltrating CD8+ T cells is commonly observed (9,11).

Given the intimate relationship between RT and immunogenic cell death, as well as the advent of immunotherapy drugs designed to uncloak tumor cells to immune surveillance, researchers are now exploring the utility of focal RT in combination with systemic immunotherapy. Although this combination is being tested in virtually all tumor subtypes, this review will be focused on data relevant to gastrointestinal malignancies.

Esophageal and gastric cancers

RT plays an important role in both the curative and palliative management of esophageal and gastric cancers, either alone or as a part of multimodality treatment. In patients eligible for surgery, the addition of preoperative chemoradiotherapy (CRT) improves overall survival (OS), progression-free survival (PFS), and negative margin rates compared to esophagectomy alone (12). Definitive CRT is potentially curative for non-operable esophageal cancers and is associated with 5-year OS of 34–59% (13-16).

Unlike for esophageal cancers the role of CRT versus chemotherapy alone for operable gastric tumors remains controversial. A systemic meta-analysis published in 2009 demonstrated that the addition preoperative or postoperative RT was associated with improved OS compared to surgery alone (17). The addition of postoperative CRT in resectable gastric cancer has been shown to improve OS and PFS with acceptable toxicity (18). However, there is also randomized evidence that perioperative chemotherapy improves OS compared to surgery alone and is another standard of care option for locally advanced gastric cancers as an alternative to postoperative CRT (19,20). Multiple trials are currently evaluating chemotherapy alone versus CRT including TOPGEAR (NCT01924819) and CRITICS-II (NCT02931890) in the preoperative setting and ARTIST-II (NCT01761461) in the postoperative setting (21-23). Definitive CRT for localized gastric cancer is reserved for inoperable patients (24). RT alone is typically utilized in the palliative setting and is effective for the majority of patients to alleviate dysphagia, bleeding, and pain (25).

The long-term outcomes remain poor for esophageal and gastric cancers with conventional therapies. Preclinical and emerging clinical data demonstrate that immunotherapy may significantly benefit at least a subset of these patients, especially when combined with RT. Additionally, 27% of gastric and 19% of esophageal carcinomas were found to express high levels of DNA damage response gene alterations. These mutations are associated with resistance to chemotherapy and RT, but may sensitize tumors to immunotherapy due to the increased mutational burden (26). Programmed death-ligand 1 (PD-L1) is expressed in 45% and 38% of esophageal and gastric cancers, respectively (27-30). The prognostic significance of PD-L1 expression remains to be defined. The expression of another less well studied checkpoint molecule, IDO-1, has been correlated with poor OS for both AC and SCC of the esophagus (31). Co-expression on IDO-1 and PD-L1 in pre-treatment biopsies of 158 Chinese patients was found to be predictive for poor pathologic complete response (pCR) and increased risk of recurrence in esophageal SCC (32).

Chimeric antigen receptor (CAR)-T cells engineered to target HER2 or the folate receptor have shown some preclinical efficacy *in vitro* and in animal models of gastric cancers (33,34). Preclinical models are currently investigating the potential of combining CAR-T cells with RT or chemotherapy in order to increase efficacy (35,36). Adoptive cellular immunotherapy with cytokine induced killer cells/dendritic cells (CIKC/DC) has also shown efficacy in esophageal and gastric cancer and can be further enhanced by RT (37,38). Priming dendritic cells of elderly patients with esophageal cancers prior to reintroducing them after RT has been shown to lead to improved response rates compared to RT alone (39).

In esophageal cancer, exposure to RT leads to increase of PD-L1 expression *in vitro* and *in vivo* (27,40). Although there are data that pretreatment PD-L1 may be considered a negative prognostic factor, increased expression after CRT may be associated with improved OS (41). Additionally, CRT has also been shown to increase the overall immunogenicity of esophageal tumors even in the absence of changes in PD-L1 expression (42). Other modulators of the immune system are also in preclinical investigation, such

as thymosin alpha 1, a synthetic amino acid peptide, which upregulates MHC1. Emerging data suggest that improved LC may result when thymosin alpha 1 is combined with stereotactic body radiation therapy (SBRT) in metastatic heavily pre-treated esophageal cancers (43). The utility of RT in combination with immunotherapy is further being investigated in metastatic esophageal cancer in an ongoing clinical trial (NCT02642809). We are awaiting results from several ongoing studies investigating the benefit from adding immunotherapy to definitive CRT in inoperable esophageal cancers (NCT03377400, NCT03437200) or adjuvant chemotherapy following standard of care treatment (44).

HCC

HCC is the most common form of primary liver cancer comprising 75–85% of cases. Most frequently seen in countries with high hepatitis B virus or hepatitis C virus infection rates it is the 6th most common cause of cancer worldwide and the 4th leading cause of cancer death (45).

Surgical resection and liver transplantation are the first line therapies for HCC; however, the majority of patients do not undergo surgery due to comorbid conditions including advanced liver cirrhosis, metastatic disease, or limited availability of donor livers (46). Locoregional therapies such as RT, chemoembolization, radioembolization, or radiofrequency ablation are alternative treatments for patients who are not candidates for surgery or who are awaiting a donor liver. Due to high rates of background liver cirrhosis, recurrence of HCC is common even after locoregional therapies (47).

Systemic therapies are often prescribed to reduce the risk of locoregional and distant disease recurrence, but their efficacy has largely been suboptimal. Traditional cytotoxic chemotherapies have limited effectiveness in HCC and are often not administrable due to underlying liver cirrhosis. Sorafenib and lenvatinib are tyrosine kinase inhibitors (TKI) that have been approved as first line systemic therapies for patients with unresectable HCC, while regorafenib and cabozantinib have been approved in the second line (47). These agents improve survival on the order of three months or less compared to placebo (47). Novel therapies are greatly needed to improve outcomes for HCC patients.

The HCC tumor microenvironment although rich with lymphocytes is predominantly immunosuppressive, thus enabling cancer cells to grow with little immune regulation. Multiple immunotherapy strategies are being studied to counteract the immunosuppressive tumor microenvironment or stimulate immune-mediated cell kill (48). In 2017, the PD-1 checkpoint inhibitor nivolumab was the first immunotherapy agent approved for the treatment of HCC based on an objective overall response rate (ORR) of 14.3% in the CHECKMATE-040 phase 1/2 clinical trial. Ninety-one percent of responders had responses lasting 6 months or longer and 55% had responses lasting 12 months or longer. Twenty-five percent of patients had a grade 3–5 treatment-related adverse event (49). In the following year the PD-1 inhibitor pembrolizumab was approved in patients that had been previously treated with sorafenib based on an ORR of 17% in the KEYNOTE-224 phase 2 clinical trial (50). The subsequent phase III randomized trial, KEYNOTE-240, comparing pembrolizumab to placebo did not meet its co-primary endpoints of OS and PFS (51), but the CHECKMATE-459 randomized trial comparing nivolumab to sorafenib as first-line therapy has yet to be reported.

The use of other checkpoint inhibitors, either alone or in combination with PD-1 inhibitors, may unlock the potential of checkpoint blockade. The CTLA-4 inhibitor tremelimumab was evaluated in a phase 1 trial for patients with HCC and showed a disease control rate of 76.4% and time to progression of 6.5 months (52). Due to the low response rates typically seen with CTLA-4 inhibitors alone it is being combined with PD-1 inhibitors with the hope of improving efficacy. The phase 3 randomized trial HIMALAYA is comparing the combination of temelimumab and the PD-L1 inhibitor, durvalumab, to sorafenib (NCT03298451). We await the results of multiple ongoing randomized clinical trials testing PD-1, PDL-1 or CTLA-4 inhibitors for HCC (NCT03794440, NCT03298451, NCT02702401, NCT02576509, NCT03755739, NCT03062358, NCT03713593, NCT03847428, NCT03764293, NCT03434379). Other checkpoint inhibitors such as, T-cell immunoglobulin and mucin domain containing-3 (TIM-3), transforming growth factor-β (TGF-β), and lymphocyte activation gene 3 (LAG-3) are also being tested in ongoing clinical trials either alone or in combination with PD-1 blockade (NCT03680508, NCT02947165, NCT03538028).

Adoptive cell transfer is the process of passively administering autologous lymphocytes following *ex vivo* cultivation in order to augment the immune response to a cancer. Three subtypes of lymphocytes are being studied for HCC: natural killer (NK) cells, cytokine-induced killer (CIK) cells, and chimeric antigen receptor T (CAR-T) cells (53). Donor NK cells stimulated by

interleukin-2 (IL-2) were shown to have no adverse events when administered to patients with cirrhosis and HCC undergoing liver transplantation (54). Ongoing clinical trials are investigating the administration of NK cells versus sorafenib (NCT03563170) and combining NK cell transfer with irreversible electroporation (NCT03008343). CIK cells are created by incubating monocytes with cytokines and a monoclonal antibody against the T cell marker CD3. CIK cells have shown cytotoxic effects against HCC *in vitro* and *in vivo* (55). A randomized phase 3 trial of CIK cell administration after RFA, ethanol injection or resection showed a 14-month improvement in recurrence-free survival (56). After gaining FDA approval for the treatment of lymphoma, CAR-T cell therapy is also being studied for the treatment of various solid tumors, including HCC. HCC commonly expresses number of tumor-associated antigens that make for potential targets for CAR-T cell therapy including, GPC-3, EpCAM and AFP (57,58). The only published trial to date for CAR-T cell therapy for HCC was an abstract of a phase I trial which demonstrated no dose-limiting toxicity and only one grade 3 adverse event (59). There are multiple ongoing clinical trials exploring the use of CAR-T cell therapy for HCC (NCT03198546, NCT03130712, NCT02715362, NCT03013712, NCT02723942).

Intrahepatic cholangiocarcinoma

Intrahepatic cholangiocarcinoma (IHC) is the second most common primary liver cancer with an incidence of 5,000 new cases in the United States each year (45). Frequently diagnosed at advanced stages, only about 20% of patients with newly diagnosed IHC are candidates for surgery. Unlike HCC, IHC is responsive to cytotoxic chemotherapies. The combination of gemcitabine and cisplatin are first-line agents for advanced IHC, and are commonly prescribed along with RT, TACE and radioembolization. Unfortunately, outcomes remain poor with long term survival infrequent due to high rates of recurrent disease.

To date, no immunotherapy agents have yet been approved for the treatment of IHC. Cancers with mismatch repair (MMR) deficiencies have been shown to have a high mutational load and respond frequently to checkpoint inhibitors. Pembrolizumab was approved for the treatment of solid tumors with MMR deficiencies, regardless of histology (60). MMR deficiency has been reported in 5–10% of IHCs (61), and MMR-deficient IHC have been shown to have an overall response rate to pembrolizumab of 53% (62). Microsatellite stable (MSS) IHCs have also shown responsiveness to checkpoint inhibitors. In a phase 2 trial testing nivolumab as a second-line agent, 55% of patients achieved stable disease or a partial response with a median PFS of 3.5 months (63).

Based on these encouraging early results, numerous clinical trials are underway testing immunotherapy strategies for the treatment of IHC. Checkpoint inhibitors, sometimes combined with other systemic agents, are being tested in multiple phase I or II trials (NCT03201458, NCT04003636, NCT03473574, NCT03250273, NCT02834013, NCT02628067, NCT03095781, NCT02393248, NCT02821754, NCT03257761), adoptive cell transfer investing CIK and CAR-T cells alone or in combination with checkpoint inhibitors or RFA are also being tested in phase I-III trials (NCT02482454, NCT03633773, NCT02757391). A phase 2 cancer vaccine trial is also underway (NCT03042182).

Due to the potential synergistic effects of RT and immunotherapy for the treatment of a variety of solid tumors seen in multiple preclinical studies, RT and immunotherapy combinations are being tested in multiple clinical trials for both HCC and IHC. The safety of SBRT followed by the checkpoint inhibitors nivolumab or ipilimumab is being tested in a phase 1 trial (NCT03203304). Nivolumab is also being combined with yttrium-90 radioembolization prior to hepatectomy in a phase I trial (NCT03812562). Sequential TACE followed by SBRT and immunotherapy is being tested in a phase 2 clinical trial to downstage HCC prior to hepatectomy (NCT03817736). Finally, a phase 2 study is investing the combination of gemcitabine, cisplatin, anti-PD-1 antibody and SBRT for the treatment of IHC (NCT03898895).

Pancreatic cancer

Pancreatic cancer ranks among the deadliest malignancies with over 45,000 individuals succumbing to this disease each year in the United States (64). Half of all patients present with metastatic disease with under a 5% probability of surviving 5 years (65,66). For those eligible for surgery, historical results have shown steady increases in 3-year survival from 14% in the 1970s, 21% in the 1980s, to 36% in the 1990s (67). Much of this improvement may be credited to refinements in surgical techniques which cut perioperative mortality from 30% in the 1970s to 1% by the 2000s (68). Nevertheless, 5-year survival with surgery alone

is estimated at only 18% (68). With advances in adjuvant therapy, median survival has climbed to almost 5 years after resection for select patients (69).

Unfortunately, only 33% of unresectable pancreatic cancers are converted to resection with neoadjuvant strategies involving RT and chemotherapy (70). Not surprisingly, the response to preoperative treatment correlates highly with survival. In a contemporary cohort of patients who underwent neoadjuvant CRT followed by surgery, limited treatment response was associated with a median survival of 26 months in comparison to over 60 months for those achieving pCR (P<0.001) (71). More importantly, only 10% of patients achieved pCR (71), emphasizing the need for therapeutic strategies to enhance pCR rates.

Given the poor results with conventional therapies for pancreatic cancer the utility of immunotherapy has garnered significant attention. Initial interest was supported by observations demonstrating a positive correlation between the presence of CD4+ and CD8+ T cells in pancreatic tumors and survival (P<0.01) (72). However, pancreatic cells create an immunosuppressive microenvironment through the secretion of a variety of factors including TGF-β, IL-10, Gal-1, and IDO (73,74). Many pancreatic tumors also express PD-L1 and have a poorer prognosis due to reduced tumor infiltrating lymphocytes, particularly CD8+ T cells (75). The tumor microenvironment is also characterized by the presence of regulatory CD4+ T cells, mast cells, tumor-associated macrophages, and myeloid-derived suppressor cells that stymie immune surveillance (76).

As a result of the poorly immunogenic microenvironment in pancreatic cancers, trials involving immunotherapy have thus far been disappointing. In contrast to many other solid tumors, anti-PD-L1 treatment has shown no response in pancreatic cancers (77). Anti-CTLA-4 monotherapy was also tested in a phase II study, and again showed no response (78). These initial results with monotherapies prompted examination of combination strategies. A recently completed phase II study compared durvalumab (a PD-L1 inhibitor) alone versus durvalumab with tremilimumab, but only showed a modest gain in the response rate from 0% to 3% with multi-agent treatment (79).

The suboptimal results from immune checkpoint inhibition have increased interest in strategies that may convert pancreatic cancers to more immunogenic tumors. One approach is through vaccination to induce the development of T cells with enhanced targeting capability. In 2014 researchers from Johns Hopkins reported results from a trial examining an irradiated, granulocyte-macrophage colony-stimulating factor (GM-CSF—secreting, allogeneic vaccine (GVAX) given as a single agent or in combination with low-dose cyclophosphamide (80). Two weeks after vaccine administration tumors were resected with specimens demonstrating the formation of intratumoral tertiary lymphoid aggregates in 33 of 39 patients with corresponding improvements in T cell trafficking and survival. GVAX has also been tested in combination with ipilimumab and found to improve median survival from 3.6 to 5.7 months compared to ipilimumab alone (81). However, when examined against standard chemotherapy, GVAX-based immunotherapy did not improve survival (82). Further research into both live and peptide-based vaccines remains ongoing.

Recently, researchers from the Medical College of Georgia noted that PD-L1 expression could be modified through a novel, epigenetic pathway (83). They first noted that human mixed lineage leukemia protein-1 (MLL1) and PD-L1 were highly expressed in many pancreatic cell lines. Then they discovered that MLL1 could bind to the H3K4me3 promoter of the *CD274* gene, and catalyze the promoter to induce expression of PD-L1 from the *CD274* gene. By inhibiting MLL1 they were able to improve anti-PD-L1 and anti-PD-1 based immunotherapy (83). This novel approach will likely move to clinical trials and stimulate additional epigenetic investigations.

Some researchers are examining RT to prime the response to immunotherapy after clinical benefits were observed with abscopal responses in melanoma (84). Preclinical data provide evidence that combining RT and immunotherapy maybe a prudent strategy for pancreas cancer. Yasmin-Karim *et al.* showed that combining RT and anti-CD40 had a more profound effect on tumor regression than either alone in a pancreatic cancer mouse model (85). Ongoing trials are evaluating checkpoint inhibitors with RT. One single arm phase 2 trial (NCT03490760) in metastatic pancreas cancer patients is exploring whether 8 Gy ×3 delivered sequentially to two different lesions with concurrent durvalumab in the second-line improves PFS compared to historical control; the intent of irradiating multiple lesions is to increase the probability of having a more robust anti-tumor response through a RT "revaccination" effect given that RT may function like an *in situ* tumor vaccine.

The ability to predict which patients develop an abscopal response is lacking. This is in part due to the complex relationship between RT and the immune system.

Although RT can induce anti-tumor effects through antigen presentation and improved lymphocyte accessibility to tumor (86), it may also induce opposing changings such as the upregulation of PD-L1 expression (7,87). At least with low dose radiation, preclinical data suggests that changes are largely favorable and enhance anti-tumor immunity (88).

An additional strategy that warrants further investigation is hyperthermia. In preclinical studies hyperthermia released heat shock proteins and chemokines that activated the immune response (89). Furthermore, hyperthermia enhances chemotherapy delivery in pancreatic cancer models by inducing tumor stromal changes that may also improve access for immune cells (90,91). RT and hyperthermia are also complimentary with tumor cells sensitive to one or the other at different points in their cell cycle. As a result, hyperthermia may be particularly valuable in a trimodality approach with RT and immunotherapy (90).

At this time there are over a dozen ongoing clinical trials examining various combinations of RT, immunotherapy and chemotherapy for pancreatic cancer. Future investigations should also incorporate strategies to improve the tumor microenvironment with hyperthermia as well as epigenetic interventions to sensitize cancer cells to cytotoxic therapies. The heterogeneous nature of pancreatic cancers will likely demand personalized combinations for each patient and continual modification of such strategies throughout their disease course.

Colorectal cancer (CRC)

Immunotherapy for CRC was first explored in the 1980s after preclinical models demonstrated the efficacy of autologous tumor cell vaccines with an adjuvant [Bacillus Calmette-Guérin (BCG)] against injected tumor cells by promoting the host's defense against tumor-specific and tumor-associated antigens. The injection of BCG with tumor cells was able to promote systemic immunity and halt tumor growth (92).

These results were subsequently evaluated in the adjuvant setting in several phase 3 randomized clinical trials comparing surgical resection only versus surgical resection followed by vaccination. In one study that enrolled 98 patients beginning in 1981 with stage II-III CRC the primary endpoints of OS and disease-free survival (DFS) for all patients were not statistically different (HR for OS 1.75, P=0.68, HR for DFS 1.58, P=0.147); however, on subset analyses, there was found to be a benefit to vaccination in patients with colon cancer (HR for OS 2.83, P=0.02; HR for DFS 2.67, P=0.39) (93). Another phase 3 trial, E5283, examined 412 patients with stage II-III colon cancer and demonstrated no differences in OS or DFS (94). In the 8701 study that evaluated 254 patients with stage II-III colon cancer, patients demonstrated a 44% risk reduction for recurrence favoring patients that received vaccination (P=0.023). Upon subgroup analyses, the impact was only seen in patients with stage 2 disease and resulted in a 61% risk reduction (95). A meta-analysis was performed including the above trials that suggested a benefit to OS and DFS (96). Currently, a phase 3 trial is underway further examining the role of vaccination in the adjuvant setting for stage 2 colon cancer patients. While vaccines have yet to alter routine clinical practice, trials are underway to better identify a subset of patients who may benefit from vaccination.

Immune checkpoint inhibitors are under active investigation for CRC and have demonstrated significant efficacy in selected patient population. Initial results with PD-1 blockade demonstrated an overall poor response amongst all CRC patients; however, a subset of patients with mismatch repair (MMR)-deficient tumors, corresponding to high levels of microsatellite instability (MSI-H), demonstrated greater response. This was hypothesized to be due to the high burden of somatic mutations that could be more easily recognized by the host immune system. The KEYNOTE-016 trial evaluated 41 patients with treatment refractory metastatic disease who were treated with pembrolizumab across 3 cohorts including MSI-H CRC (n=11), mismatch repair-proficient CRC (n=21), and MSI-H non-colorectal tumors (n=9). Objective response rates (ORRs) were 40%, 0% and 71%, respectively across the three cohorts. Median PFS and OS were not reached in the MSI-H cohort compared to 2.2 months and 5.0 months, respectively, for the mismatch repair-proficient cohort (HR for PFS 0.1, P<0.001; HR for OS 0.22, P=0.05) (97).

These results have led to both the KEYNOTE-164 trial examining response to pembrolizumab in patients with pretreated metastatic MSI-H CRC and the phase 3 randomized KEYNOTE-177 comparing pembrolizumab to investigator choice chemotherapy. Interim results from the KEYNOTE-164 trial including 63 patients at a median 12 months follow up demonstrated an ORR of 32% with median PFS of 4.1 months (98,99).

Combination immune checkpoint inhibition is another treatment strategy currently under investigation. The phase 2 CHECKMATE-142 trial investigated nivolumab with or without the addition of ipilimumab for treatment of patients with previously treated metastatic MSI-H or MSS CRC. Among the MSI-H cohort, ORR was 31.1% for patients

treated with nivolumab alone (n=74) and 55% for those receiving combination nivolumab and ipilimumab (n=119). 12-month PFS and OS were 50% and 73%, respectively, in the nivolumab alone cohort and 71% and 85%, respectively, in the combination therapy cohort. Treatment response was observed in patients independent of tumor or immune-cell PD-L1 expression, clinical history of Lynch syndrome, or BRAF and KRAS mutation status (100,101).

Further results from the CHECKMATE-142 trial regarding patients with MSS disease are forthcoming; however, results from numerous trials have failed to show significant responses with response rates for MSS patients treated with nivolumab or nivolumab and ipilimumab of 10% or 0%, respectively. Thus, other strategies are under investigation to identify other potential immunotherapies. A cohort of 23 patients with metastatic CRC were treated with a combination of atezolizumab, an anti-PD-L1, and cobimetinib, a MEK-inhibitor. MEK inhibition in preclinical models have demonstrated increased anti-PD-L1 activity through increased CD8+ T-cell tumor infiltration and MHC-1 upregulation. The ORR was 17% with 4 partial responders, 3 of which were MSS (102). A phase 2 trial combining ipilimumab and nivolumab with RT in metastatic MSS CRC is currently under investigation and has enrolled 40 patients. RT induces cellular damage within the tumor which may increase responsiveness to immunotherapy. Of the 24 patients who received RT, the ORR was 12.5% and median duration of disease control was 77 days (103). Other combination strategies including anti-VEGF or chemotherapy are also under investigation.

Anal cancer

Anal SCC is highly associated with high-risk subtypes of the human papilloma virus (HPV). In addition to its oncogenic properties, HPV proteins E6 and E7 promotes tumor infiltration by lymphocytes and can trigger an anticancer host immune response, increasing interest in investigation of the role of immunotherapies in the disease (104).

Recent studies have been published investigating the safety and efficacy of PD-1 checkpoint inhibitors in treatment refractory anal cancer. KEYNOTE-028 was a phase IB multicohort trial assessing pembrolizumab in patients with treatment refractory, PD-L1 positive solid tumors. Twenty-four patients with anal SCC were enrolled and 88% of patients were pretreated. The ORR was 17% and an additional 42% of patients had stable disease with a median duration of 3.6 months. Median PFS and OS were 3.0 months and 9.3 months, respectively (105). Similarly, the NCI9673 phase 2 study investigated the safety and efficacy of nivolumab in 37 patients with treatment refractory metastatic anal cancer. 86% of patients had been pretreated with a platinum-based chemotherapy and the ORR was 24% with 7 partial responses and 2 complete responses. Median PFS and OS were 4.1 months and 11.5 months, respectively with 48% of patients alive at 1 year (106). Both regimens were well tolerated without unexpected adverse events. Additionally, nivolumab with or without concurrent ipilimumab, an anti-CTLA-4 antibody, is currently under investigation in patients with treatment refractory metastatic anal squamous cell carcinoma (NCT02314169) and pembrolizumab alone is currently being evaluated in patients with progressive advanced solid tumors including anal squamous cell carcinoma after prior treatment failure (NCT02628067).

Integrating immunotherapy with standard combined modality therapy including radiation and chemotherapy is an area actively under investigation to evaluate the safety and potential synergistic effects of treatment. There is a current trial investigating the role of nivolumab following completion of standard concurrent chemoradiotherapy for high risk stage II-IIIB anal squamous cell carcinoma (NCT03233711). In addition, there was a recent trial evaluating the role of Listeria-based immunotherapy given concurrently with mitomycin and cisplatin-based chemoradiation. Ten patients with localized anal squamous cell carcinoma were enrolled and 9 patients completed concurrent treatment. All 9 patients had a complete clinical response and 8 patients were free from progression at a median follow up of 42 months (107).

Conclusions

Immunotherapy is changing the treatment paradigm for many cancers, and there is increasing evidence that patients with gastrointestinal cancers may benefit. Combining immunotherapy and RT may be an effective strategy to increase the overall anti-tumor immune response for gastrointestinal cancer patients, although further evaluation is needed in order to better understand predictors of response, mechanisms of treatment resistance, and biomarkers of toxicity.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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