Developing rational combinations of immune checkpoint inhibitors and radiation therapy for gastrointestinal cancers

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Abstract: Evidence supporting the synergistic antitumor activity of radiation therapy combined with immune checkpoint inhibitors is rapidly growing. Investigators should consider the characteristics and challenges of gastrointestinal (GI) cancers to evaluate the safety and clinical effectiveness of this combination. In this paper, we present the rationale for exploring this strategy and the opportunities it possesses to challenge our standard of care. We also discuss unique considerations to systematically develop this combination in GI cancers.

Keywords: Radiation therapy; immunotherapy; chemoradiation; radiation oncology; gastrointestinal cancer

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Introduction

The United States (US) Food and Drug Administration (FDA) approved the first immune checkpoint inhibitor, ipilimumab, for metastatic melanoma in 2011. By the end of 2016, immune checkpoint inhibitors had additional FDA indications for melanoma, non-small cell lung cancer, renal cell cancer, Hodgkin lymphoma, head and neck cancers and bladder cancer (1). In addition, a broad range of additional treatment strategies to harness the immune system to treat cancer are in development including cancer vaccines, oncolytic viruses and monoclonal antibodies targeting various receptors with immune modulatory function (2-6).

Cancers of the gastrointestinal (GI) tract have not seen early wins in this field. However, early phase clinical trials suggest potential activity in hepatocellular cancer, gastro-esophageal and anal cancer (7-10). Mismatch repair enzyme deficiency status may predict clinical response to the anti-programmed death-1 immune checkpoint inhibitor, pembrolizumab (11). A higher rate of potential mutation associated neoantigens in mismatch repair deficient tumors, compared with mismatch proficient cancers, has been proposed as a potential mechanism to explain this finding. One strategy to overcome the immunosuppressive phenotype of cancer is to combine checkpoint inhibitors with radiation therapy. Radiation therapy is routinely applied for the management of GI cancer patients and has recognized immune stimulatory effects. In this paper we present the rationale of combining radiation therapy and checkpoint inhibitors for GI cancers including the opportunities it possesses to challenge our standard of care. We also present a strategy to systematically develop this combination in the clinic.

Radiation, cancer, and the immune system

Radiation therapy can overcome tumor related immune suppression through a number of mechanisms. These include (I) induction of a pro-inflammatory tumor environment and enhanced maturation of dendritic cells, (II) increase in tumor antigen load from cell death, and (III) enhanced cross-presentation of tumor antigens (12-14).

Stereotactic body radiation therapy (SBRT) is increasingly utilized for clinical care across multiple indications. SBRT utilizes hypofractionated courses of

radiation therapy, delivered with high dose-per fraction using advanced image guidance (15). SBRT has been shown to be a safe and effective treatment for multiple tumor types and sites (16-18). The immune stimulating effects of radiation may be made more prominent when high radiation doses and short courses of therapy, both key features of SBRT, are utilized (19). Clinically, the immunomodulatory effect of radiation therapy in cancer is most strikingly manifested as tumor responses in lesions distant from the targeted site: the 'abscopal effect'. *In vivo* animal studies have demonstrated that the abscopal effect of radiation therapy is, at least in part, immune-mediated (20-22). Abscopal effects are clinically identifiable and have been reported following radiation in melanoma, non-small cell lung cancer and renal cell carcinoma (23-25).

Checkpoint inhibitors and radiation therapy

There is mounting evidence that immune checkpoint inhibition synergizes with radiation. Programmed death receptor 1 (PD-1) and its ligand (PD-L1) interact to protect tumor cells from lysis by cytotoxic T lymphocytes (26). Anti-PD-1 and anti-PD-L1 antibodies block this interaction and activate the immune system in a non-specific manner leading to an antitumor response. Preclinical studies have supported the augmented effect of SBRT and checkpoint blockade (27). Radiation therapy may provide a specific direction to the immune response by promoting tumor-specific antigen presentation.

Sequencing radiation therapy with systemic therapy and the numbers of fractions can affect the degree of immune response to treatment. In preclinical carcinoma models multiple fractions, but not single-dose radiotherapy, resulted in an abscopal effect when combined with anti-CTLA-4 antibody (28). In the clinic, an abscopal response to radiation therapy in a melanoma patient who had initial progression on check point inhibitor was examined and provided insight into possible mechanisms of action (25). Biomarker analysis on this patient demonstrated correlative changes to antibody responses to cancer antigens, changes in peripheral blood immune cells and increases in antibody responses to other antigens. An analysis of an excised, non-irradiated, lymph node in a non-small cell lung cancer patient treated with combination therapy demonstrated increased tumor infiltrating lymphocytes (23). The above studies represent a growing body of literature in support of mechanistic synergy between radiation therapies and check point inhibitors.

GI malignancies, immunotherapy, and radiation therapy: considerations for the clinic

Selection of patients

Combining radiation therapy with checkpoint inhibitors can augment the antitumor response, and also improve tolerability of treatment by allowing de-escalation of the individual treatments. A significant concern in combining radiation and immunomodulating systemic therapies is the induction of anti-self/autoimmune responses. Early results indicate that combining immune checkpoint inhibitors and SBRT appears safe and tolerable. A retrospective review of 53 melanoma patients receiving radiation therapy and anti-PD-1 therapy including 21 patients receiving whole brain radiation showed no increase in toxicity with combination therapy (29). A prospective, phase 1, trial of SBRT and ipilimumab similarly demonstrated safety and encouraging signs of clinical activity (30). Due to differences in tumor immunogenicity and patient characteristics the rate and spectrum of toxicities in GI cancer patients undergoing combined treatment with radiation and checkpoint inhibitors may differ from those seen in other disease types such as lung cancer, melanoma or renal cell carcinoma. As an example, increased ALT was reported in 7% of patients with colorectal cancer and other cancers with mismatch repair deficiency (11). These rates in GI cancers are higher than those reported in melanoma and lung cancer (1.1% and 2.2% respectively) (31,32).

The promises, and potential pitfalls, of combination therapy can be demonstrated in the treatment of hepatocellular carcinoma (HCC). Liver-directed and systemic therapies can have significant effect in HCC patients who have compromised hepatic function due to underlying hepatic cirrhosis, prior liver directed therapy and replacement of hepatic parenchyma by tumor. Another consideration is of hyper-progressive disease, where a fraction of patients can develop accelerated tumor progression while under treatment with checkpoint inhibitors (33). The most common toxicities in a Phase 1/2 clinical trial of a checkpoint inhibitor in patients with hepatocellular cancer were fatigue, pruritus, rash and diarrhea while the most common laboratory adverse event was elevated transaminases—an accepted laboratory surrogate for hepatocyte damage. In the dose escalation phase (n=42 patients) 21% patients experienced an elevation of AST, and 15% in ALT. These rates were lower in the dose expansion phase (n=214) where AST increase was experienced in 7%, and ALT in 8%. Initial concerns

of activation of underlying viral infection in hepatitis patients with hepatocellular cancer have not borne out to be clinically significant (34). There was no apparent difference in the rate of these adverse events based on etiology of hepatitis. The risk of hepatic decompensation in patients with borderline liver dysfunction, specifically in patients with HCC, is real, and may be exacerbated by the concomitant or sequential use of radiation therapy, including SBRT. Moreover, the rate of AEs in clinical trials may under-represent those of the real world setting due to factors related to inclusion and exclusion criteria. Combining checkpoint inhibitors with radiation therapy may reduce the required dose of checkpoint inhibitors to obtain clinically meaningful responses. De-escalation may reduce the subsequent toxicities which can have significant implications in patients with baseline compromised organ function.

Therefore, investigators and clinicians should select GI cancers patients based on the complex interaction of characteristics which can affect the safety and effectiveness of combining radiation therapy with checkpoint inhibitors. These include the patient organ function, comorbid conditions, previous cancer treatments as well as prior cancers and individual patient risk factors.

Radiation dose-fractionation and target volumes

Anatomic structures adjacent to GI cancers affect the treatment constraints and risk of short and long term toxicity. SBRT is, in part, characterized by tumor-directed treatment without "elective" treatment of nearby tissues such as draining lymph nodes, whereas more conventional radiation treatment volumes tend to be large and incorporate tissues outside of the radiographically evident tumor. Conventional radiation/chemoradiation treatment courses for esophageal, rectal, anal cancers all are typified by treatment of elective nodal volumes. Whether such large-volume irradiation courses, as well as repeated daily treatments for many weeks, are compatible with checkpoint inhibitor and other immunomodulatory drug therapies, is not yet established. Risks for increased normal tissue injury as well as decreased efficacy of combination treatment by deleterious effects on effector immune cells and antigen presentation in lymph nodes must be considered. Target volumes may need to be considered as a variable in future clinical trials evaluating combination therapies. Similarly, selection of dose-per-fraction and number of fractions (which are often related/selected by the size of the target volume) in combination therapies will also have to be considered.

Sequencing of treatment

The optimal sequencing of checkpoint inhibitors with radiation will depend on tumor characteristics and goals of treatment. Upfront radiation can prime the immune system by release of neoantigens prior to starting checkpoint inhibitors (35). The abscopal effect of radiation therapy detailed earlier was described in patients on prior checkpoint inhibitors who received radiation therapy on progression (25). However, a staged, stepwise incorporation of radiation therapy during the entire course of checkpoint inhibition may be pertinent for others. As an example, patients on palliative systemic therapy for metastatic disease who are anticipated to be on therapy for extended periods of time are at risk of developing T-cell exhaustion. T-cell exhaustion is characterized by an acquired T-cell dysfunction due to persistent antigen stimulation as seen in chronic infection (36,37). However radiation therapy and checkpoint inhibitors lead to clinical responses through distinct and non-redundant effects on T-cell receptor (TCR repertoire), T-regulatory cells (Tregs) and T-cell exhaustion (38). Radiation therapy can be used to selectively treat high risk or symptomatic lesions, leading to tumor cytoreduction, palliation of local effects of the tumor, while concurrently helping to overcome T-cell fatigue and resistance.

Selection of end points

End points for clinical trials designed to evaluate the combination of radiation therapy and checkpoint inhibitors require careful consideration. It is reasonable to expect that lesions treated with radiation therapy will have good local control. Response of non-target lesions could be a result of abscopal effect or systemic effect of checkpoint inhibitors, but differentiating these mechanisms from one another other may not be as clinically relevant. Clinical trials for GI cancer have typically avoided response-rate based end points, except in single arm studies to gain an early indication of clinical activity, and confirmation is typically needed in larger studies. Further, immune specific response rates can be confounded by pseudo-progression or hyper-progressive disease making response rate based end points difficult to interpret. Therefore, for clinical trials assessing the activity of combining radiation therapy and immune checkpoint inhibitors, survival end points (progression free

survival and overall survival) are likely to be more relevant and less prone to biases discussed above. After the safety of combinations is determined, effectiveness of therapy should be evaluated in a randomized setting. These metrics of survival based end points and randomized studies are likely to increase the costs and duration of these trials, but given the cost and risk of toxicity is well warranted.

Combination trials offer the opportunity to explore surrogate end points in phase 2 clinical trials. Examples of areas of clinical need where surrogate endpoints, such as clinical complete response rate, can be very clinically relevant are early stage cancers being treated with neoadjuvant chemoradiation such as rectal adenocarcinoma and esophageal squamous cell carcinoma. A subset of rectal cancer patients with clinical complete response to neoadjuvant chemoradiation may be eligible for a potential non-operative 'surveillance only' approach (39). Long term outcomes are generally excellent for patients with complete response to chemoradiation (40). However the rate of complete clinical response after neoadjuvant therapy for rectal cancer is only between 8% and 10% (41,42). Surgery after chemoradiation for squamous cell esophageal cancer does not improve overall survival compared with chemoradiation alone (43,44). Local control rates in the surgery groups were higher, but at the cost of higher treatment related morbidity and mortality. Aiming to exploit the synergy between checkpoint inhibitors and radiation therapy can be a promising strategy to increase the rate of local control in early stage GI cancers and will continue to evolve in the coming years.

As mentioned previously, combining checkpoint inhibitors with radiation therapy may provide an opportunity to de-escalate the required dose and expand utilization for patients in whom the safety of checkpoint inhibitors has not been previously established. Due to a risk of exacerbating their underlying disease, patients with autoimmune disease have been routinely excluded from checkpoint inhibitor clinical trials. In the real world setting this may represent between 14% and 25% of eligible patients and close monitoring and clinical vigilance for immune related adverse events in this patient population is needed (45,46). Combining checkpoint inhibitors and radiation therapy may provide an opportunity to reduce the dose or duration of checkpoint inhibitor treatment with significant impact on patient outcomes.

Conclusions

Radiation, with its myriad and pleiotropic effects on tumor inflammation, may be an excellent partner with checkpoint inhibitors and other, similar, drugs to reverse the immunosuppressive character of these cancers. Many questions remain. For now, chief among them are sequencing and selection of appropriate radiation dose-fractionation schemes that may best integrate with immunomodulating drugs. Rational, hypothesis driven, clinical trials are needed to define the optimal dose, sequencing and clinical indications. The opportunity to deintensify therapy can have unique impact on short and long term toxicities as well as cost of care. Checkpoint inhibitors are now incorporated into the routine clinical care of lung cancer, melanoma and genitourinary cancers. Due to unique tumor and patient characteristics, GI cancers are potentially well positioned to benefit from these advancements. Combining radiation therapy with immune checkpoint inhibitors may expand their clinical application with meaningful impact for patients with GI cancers. The potential impact of effective radiation-immunomodulating therapy combinations are substantial, and worthy of our attention.

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Footnote

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

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