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AIM AND SCOPE

World Journal of Gastrointestinal Oncology (*World J Gastrointest Oncol*, *WJGO*, online ISSN 1948-5204, DOI: 10.4251) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGO covers topics concerning carcinogenesis, tumorigenesis, metastasis, diagnosis, prevention, prognosis, clinical manifestations, nutritional support, molecular mechanisms, and therapy of benign and malignant tumors of the digestive tract. The current columns of *WJGO* include editorial, frontier, diagnostic advances, therapeutics advances, field of vision, mini-reviews, review, topic highlight, medical ethics, original articles, case report, clinical case conference (Clinicopathological conference), and autobiography. Priority publication will be given to articles concerning diagnosis and treatment of gastrointestinal oncology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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EDITORIAL

Immune blockade inhibitors and the radiation abscopal effect in gastrointestinal cancers

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Abstract

The field of tumor immunology has produced in the recent years a revolution in cancer therapeutics putting an end in the long lasting frustration of investigators in the area stemming from largely unsuccessful strides to develop cancer vaccines. This progress has come from the introduction of immune checkpoint inhibitors, monoclonal antibodies blocking ligand/receptor pairs with inhibitory effects for immune cells. Through this blockade immune checkpoint blockers are able to activate the immune system and create an anti-tumoral effect. A significant sub-set of patients with various types of cancers such as melanoma, lung carcinomas and urothelial cancers benefit from treatment with these drugs and survivals have improved in some cases. However other cancers are primarily resistant to immune blockers and secondary resistance is also the norm. Radiation therapy is often used in the palliative treatment of patients with advanced cancers and, in addition to the local effect in the irradiated field, it may in rare cases produce a systemic antitumor effect, termed "abscopal". This effect has been suggested to be produced by immune mechanisms. Thus an opportunity presents for a synergistic effect of immune stimulation between radiation and immune blockade inhibitors. The therapeutic opportunities presented with the combination of radiation and these drugs for gastrointestinal cancers will be discussed in this editorial overview.

Key words: Abscopal effect; Radiation; CD28/cytotoxic T-lymphocyte antigen-4; Immune blockade inhibitors; Programmed death 1; Programmed death ligand-1

Core tip: Immune checkpoint inhibitors activate the immune response to tumors by blocking inhibitory

receptor pairs. Radiation treatment may also promote anti-tumor immune response. Thus, there exist an opportunity for synergy between the two treatment modalities that may be exploited therapeutically in gastrointestinal and other cancers.

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INTRODUCTION

Immune blockade inhibitors are a new class of anti-cancer drugs introduced over the last few years and moved to the first line treatment of some metastatic cancers as well as later line treatment of several others. Their indications expand with a quick pace and they are currently actively studied in the adjuvant setting. Their effectiveness has improved the outcomes of cancers such as metastatic melanoma and lung carcinomas, prolonging survival by several months[1-3]. Most impressively there is a significant minority of metastatic patients treated with immune blockade inhibitors who obtain long-term disease control[1-4].

The currently approved immune blockade inhibitors are monoclonal antibodies targeting CD28/cytotoxic T-lymphocyte antigen-4 (CTLA-4) or the programmed death-1/programmed death ligand-1 (PD-1/PD-L1) pair of immune blockade molecules[5]. CTLA-4 inhibitors include ipilimumab and tremelimumab while inhibitors of the PD-1/PD-L1 pair include pembrolizumab, nivolumab (anti-PD-1), durvalumab, avelumab and atezolizumab (anti-PD-L1). Each one of these drugs has its own approved indications[6]. The mechanism of action of these inhibitors involves re-enforcement of the cytotoxic activity of immune effector cells [cytotoxic T lymphocytes (CTLs) and NK cells] against tumor cells, by neutralizing inhibitory immune receptors expressed by tumor cells and antigen presenting cells. Both CTLs and NK cells may have cytotoxic effects that include targeting of cancer stem cells, believed to be at the root of cancer resistance to various therapies[7,8]. Immune blockade inhibitors are overall well-tolerated and many patients are able to receive treatment without adverse effects for several months or even years. Immune adverse effects are not uncommon, though, and they have to be recognized and treated promptly. The most common such effects reported in phase Ⅲ trials include pneumonitis, colitis, hepatitis, endocrinopathies and immune-mediated nephritis.

Radiation therapy is often used in metastatic cancers to control disease threatening vital organs such as the spinal cord or to palliate intractable symptoms such as pain. Radiation treatment schedules in the palliative and metastatic setting tend to be shorter than definite or adjuvant treatments. Single fractionation treatments have become popular in the palliation of bone metastases due to their efficacy, convenience for the patient and cost effectiveness[9].

It has been recognized for some time that, besides the local tumoricidal effect that takes place within the field applied, radiation therapy may have a systemic anti-cancer effect that affects cancer deposits outside the radiation field. This is termed the abscopal (off-target) effect. This effect is produced by the local radiation treatment which leads to production of new antigens through its tumoricidal effect. These antigens stimulate incoming immune effector cells and promote the systemic immune response to tumors through augmentation of the immune killing of tumor deposits in locations other than the irradiated tumor[10].

Despite impressive results in some cancers, most patients, including the majority of patients with gastrointestinal (GI) cancers, do not respond to immune blockade inhibitor treatments. This paper will briefly discuss immune blockade inhibitors in GI cancers and explore ways to increase their responsiveness to the drugs using the abscopal effect of radiation.

IMMUNE BLOCKADE INHIBITION IN GI CANCERS

Immune blockade inhibitors have been studied in clinical trials for all major GI cancers. Representative results of the most advanced stage trials in different GI cancers are discussed in this section. A randomized phase Ⅲ trial of nivolumab versus placebo in metastatic gastroesophageal cancer patients that had received or were intolerant to two previous lines of chemotherapy was conducted in three Asian countries (Japan, South Korea and Taiwan) and showed an 1-year overall survival (OS) of 26.6% with nivolumab versus 10.9% with placebo[11]. Median OS increased by about a month from 4.14 mo in the placebo arm to 5.32 mo in the nivolumab arm. This difference, although modest, was statistically significant.

An initial phase Ib study of pembrolizumab focused on patients with PD-L1-positive metastatic gastric and gastroesophageal junction adenocarcinoma, defined as 1% or more positive cells (both cancer and inflammatory cells countable)[12]. Partial responses were observed in eight of the 36 (22%) evaluable patients. The median OS was 11.4 mo and a subset of patients remained on treatment for more than 6 mo. Pembrolizumab was also investigated in an extensive phase Ⅱ study that included a cohort of 259 gastroesophageal cancer patients from both Asian and western countries in the third line metastatic setting[13]. Response rate (RR) was 11.6% and an additional 16.2% of

patients had stable disease. The study included both PD-L1-positive and PD-L1-negative patients and RR was higher in PD-L1-positive patients. In addition, in a small subset of patients that had tumors with microsatellite instability (MSI), RR was 57%[13]. The anti-PD-L1 antibody avelumab was investigated in a phase Ib trial in patients with metastatic gastric cancer in the second line setting[14]. This study which has only been published in an abstract form included also an arm with 89 patients receiving avelumab treatment as maintenance after chemotherapy. The median duration of treatment in this arm was about 3 mo with a range from 2 wk to over a year.

In hepatocellular carcinoma, nivolumab has been approved by the American Food and Drug Administration in the fall of 2017 for patients with disease not amenable to curative surgery or local treatments, with or without hepatitis B or C and treated previously with sorafenib. Approval was based on a phase Ⅰ/Ⅱ escalation/expansion trial that showed an overall RR of 14.3%[15]. In most responders the duration of response was longer than 6 mo and in half of the responders it lasted for over a year. The anti-CTLA-4 antibody tremelimumab was shown in a phase Ⅰ study of 20 patients with hepatocellular carcinoma and hepatitis C-associated liver cirrhosis Child-Pugh grade A or B to produce partial responses in 17.6% of evaluable patients (3 of 17)[16]. Median OS was 8.3 mo. Trials with other immune checkpoint inhibitors are ongoing as well as a randomized trial of nivolumab versus sorafenib in the first line setting.

A small phase Ib/Ⅱ study of pembrolizumab with chemotherapy (nab-paclitaxel and gemcitabine) in metastatic pancreatic cancer has included 17 patients of whom eleven were evaluable for response in the phase Ⅱ part[17]. A partial response or stable disease was obtained in all patients for a disease control rate of 100%. Median OS was 15 mo. Several other trials are ongoing in pancreatic cancer to clarify the clinical benefit of immune blockade inhibitors in this disease which still has grim prognosis.

Results of immune blockade inhibition as monotherapy in colorectal cancer as a whole are not encouraging. However, the subset of colorectal cancers with mismatch repair defects (dMMR) and MSI display a higher sensitivity to immune blockade inhibitors. In a phase Ⅱ trial of pembrolizumab in patients with metastatic colorectal cancer the objective RR was 40% in patients with dMMR and 0% in patients with proficient mismatch repair (pMMR)[18]. Median OS was not reached in dMMR patients and was 5 mo in pMMR patients. Similarly in a phase Ⅱ study of nivolumab that included only metastatic dMMR or MSI colorectal cancer patients the objective RR was 31% and the disease control rate at 12 wk or longer was 51%[19]. The combination of nivolumab with ipilimumab was even more effective in metastatic dMMR or MSI colorectal cancer patients producing a RR of 55% and disease control rate at 12 wk or longer of 80%[20].

Given these results and similar encouraging efficacy in non-colorectal cancers with dMMR and high mutation load tumors[18], the American FDA has granted pembrolizumab with the first indication for use in any solid tumor with MSI/dMMR independently of primary site. Mutation load arises, thus, as a marker of effectiveness to checkpoint inhibitors independently of the underlying defect that creates this increased load. Besides MSI/dMMR, other genetic defects, such as mutations in polymerases ε (POLE) and δ1 (POLD1) may result in high tumor mutation load[21]. These results and the fact that even among MSI/dMMR patients only a subset derive clinical benefit from immune checkpoint inhibitors illustrate the point that there is a need for further prognostic markers development in immune checkpoint inhibitors therapeutics. Improvement in characterization of responsive tumors may also help in discovering ways of inducing sensitivity in initially resistant tumors and tumors with acquired resistance.

MOLECULAR PATHOGENESIS OF THE ABSCOPAL EFFECT

Double strand DNA (dsDNA) released in the cytoplasm of irradiated cells activates cGAS (cGMP-AMP synthase), an enzyme that synthesizes cyclic GMP-AMP (cGAMP). This and other dinucleotides activate protein STING (stimulator of interferon response) which results in production of type Ⅰ interferons (type Ⅰ IFNs) through the action of transcription factors IRF3 and NF-κB and concomitant up-regulation of MHC Ⅰ molecules and danger signals[22,23]. Type Ⅰ IFNs act in an autocrine and paracrine manner to promote the inflammatory environment that may result in an anti-tumor response, if additional conditions are fulfilled. These conditions include tumor antigen presentation by the cancer cells and absence of inhibitory signals that inhibit incoming immune effectors. Activated immune effector cells can kill tumors locally but also by travelling to other locations where tumor cells expressing the same antigens exist.

Ligation of PD-1 inhibitory immune receptor may have a negative effect in the development of abscopal effect[24]. In a pre-clinical study in mice bearing tumors in two different locations, of which only one was irradiated with a single dose of 15 Gy, the abscopal effect observed in the non-irradiated tumor was stronger in mice receiving an anti-PD-1 antibody or mice that were knock-out for the PD-1 receptor than in control mice. Interestingly, PD-1 knock-out or antibody-treated mice had also a better response in the primary tumor site. In contrast, no difference was observed in a secondary tumor consisting of a different cell line from the one at the irradiated site, suggesting that activation of immune cells has to take place in the context of the relevant

antigen presentation and not in the context of antigens from a different tumor[24]. Thus, the combination of the two treatments, radiation and PD-1 inhibitors, presents an opportunity of synergy, mediated by the local radiation-induced activation of immune cells and in parallel neutralization of inhibitory receptors by immune blockade inhibitors.

The dose of radiation treatment has been proposed to be of importance in the production or lack of abscopal effect. Experiments in mice showed that radiation treatment at a dose of 24 Gy in three fractions of 8 Gy each, in combination with an anti-mouse CTLA-4 monoclonal antibody was effective in inducing an abscopal effect in breast cancer xenografts[25]. In contrast, a single fraction of 20 Gy was ineffective in inducing an abscopal effect, despite synergistic effects in control of the irradiated site that were similar. Use of five fractions of 6 Gy each was also successful in inducing an abscopal effect[26]. Colon cancer xenografts exhibited similar behavior, responding in remote sites only when the radiation was fractionated. The differential effectiveness of different radiotherapy fractionations was traced to induction of DNA exonuclease Three prime Repair Exonuclease 1 (TREX1) by the higher radiation dose. Activated TREX1 cleaves cytoplasmic dsDNA, preventing cGAS activation and induction of the type Ⅰ IFNs response. A single dose of 12 to 15 Gy or above was shown to induce TREX1 in different cell lines and a decrease in dsDNA production post-irradiation was observed in parallel[25,27].

The timing of radiation treatment in relation to immune checkpoint inhibitors administration may be also relevant for obtaining an optimal abscopal effect[28]. For example, when radiation precedes immune checkpoint inhibitors administration, it may help produce antigens that could serve as targets for the revitalized immune system. Conversely radiation therapy in patients already receiving immune checkpoint inhibitors may diversify antigens available for presentation and prevent immune exhaustion[29]. These scenarios remain speculative as timings of the two treatments has not been directly examined and compared and further study of the optimal timing of the combination and whether it is critical is warranted.

ABSCOPAL EFFECT OF RADIATION THERAPY IN GI CANCER PATIENTS RECEIVING IMMUNE CHECKPOINT INHIBITORS

A few clinical studies that had included patients with GI cancers and described the abscopal effect of radiation therapy in patients receiving also immune checkpoint inhibitors have been published.

A radiation- ipilimumab combination phase Ⅰ study of 35 patients with various cancers included seven patients with GI cancers (4 colorectal, 2 gastroesophageal and 1 cholangiocarcinoma)[30]. Patients received stereotactic ablative radiation therapy (SABR) to a total dose of 50 Gy in four fractions or 60 Gy in 10 fractions starting after the first or second dose of ipilimumab which was given at a dose of 3 mg/kg every 3 wk for 4 doses. Organs irradiated included the liver and the lung. Among the 31 assessable patients, three patients (10%) had an abscopal partial response and four additional patients had stable disease in non-irradiated lesions lasting at least 6 mo for a clinical benefit rate of 23%[30]. Patients who derived clinical benefit from the radiation-immunotherapy treatment had an increased ratio of circulating CD4+/CD8+ lymphocytes as well as an increase in expression of receptors 4-1BB and PD-1 in CD8+ lymphocytes. It is not possible from the published report to derive the specific responses of patients with GI cancers.

A report of patients with metastatic cancers that were treated in a trial of the monoclonal anti-PD-L1 antibody durvalumab and concomitantly received radiation therapy for palliation of pain or compression symptoms or for dissociated progression of their disease included four patients with colon cancer[31]. No evidence of abscopal activity was observed in any of these patients or any of the six patients with other cancers that were included in this report.

The tolerance of combination of immune checkpoint inhibitors and radiation therapy has been documented and no unexpected adverse effects have been observed[30-32]. The irradiated organs do not show increased incidence of immune mediated adverse effects with either anti-CTLA-4 or anti-PD-1 monoclonal antibodies[32]. Acceptable tolerance notwithstanding, these very early data suggest that there is significant room for improvement in the efficacy of combinations of immune checkpoint inhibitors and radiation therapy in GI cancers.

PERSPECTIVE: RADIATION ABSCOPAL EFFECT TO IMPROVE EFFICACY OF CHECKPOINT INHIBITORS IN GI CANCERS

Given that the radiation abscopal effect has an immunologic pathogenesis, and concomitantly checkpoint molecules are up-regulated in irradiated tissues, the combination of inhibitors blocking PD-L1, PD-1 or CTLA-4 has the potential to act synergistically with radiation[33]. The combination of radiation therapy with immune blockade inhibitors to boost immune-mediated effects is under investigation[34,35]. The potentiation of the efficacy of checkpoint inhibitors in GI cancers with high mutation burden, such as MSI-H colorectal cancers, by radiation therapy would be derived from a better priming of effector immune cells in the inflammatory environment

of irradiated tumors where the absence of checkpoint inhibition would negate the restrain of immune cells normally produced by immune checkpoint molecules up-regulation, as well as activation of incoming effector immune cells by inhibition of inhibitory receptors in other tumor locations[36]. In the other hand, tumors with low mutation burden may require additional treatments such as chemotherapy to boost the radiation effect and increase their immunogenicity and presentation of antigens to the activated immune effectors. Mutation burden may not be the only determinant of immune blockade inhibitors efficacy. For example, EBV-positive gastric cancers are MSS and possess low mutation burden but display a high immune infiltration and a tumor environment with high expression of PD-L1[37]. In addition, immune cells in EBV-positive as well as MSI-H gastric cancers were observed to penetrate in tumors, in contrast to MSS, EBV-negative gastric cancers where immune cells remained in the periphery of tumors[38]. A case of an EBV-positive gastric cancer patient who derived benefit from treatment with the checkpoint inhibitor avelumab was recently reported illustrating the above points[37]. Additional predictive biomarkers for response to immune checkpoint inhibitors combinations with radiotherapy would certainly help optimize treatment.

The aforementioned fractionation dose of radiation effect on production of abscopal effect deserves to be more studied in clinical trials for fractionation optimization. Moreover, besides effects on tumor cells, radiation has direct effects on lymphocytes that happen to be in the radiation field and thus may be adversely affected or killed. Lymphocytes are more sensitive in doses of radiation lower than those that have tumoricidal effect and inadvertent immunologic effect of radiation will have to be taken into consideration when designing optimal schedules. This could be more critical if more extensive fields or fields including significant amount of lymphatic tissue are used.

The organ irradiated may also have implications for an optimal production of an abscopal effect. Some studies have shown that a greater abscopal effect may be produced when liver is irradiated compared to irradiation of lung[30]. The mechanism may involve enhanced production of cytokines from irradiated hepatic resident cells that could produce a systemic immune-promoting effect. As a result, a systemic abscopal effect would not be expected to be identical in different clinical radiation scenarios and this would have to be incorporated in the design of combination studies.

Clearly further studies will be needed for the optimal determination of indications for use of immune checkpoint inhibitors in GI cancers, based on biomarkers and the optimal incorporation of radiation treatment parameters in order to harness the abscopal effect.

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