Radiation and checkpoint blockade immunotherapy: radiosensitisation and potential mechanisms of synergy

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Checkpoint blockade immunotherapy has received mainstream attention as a result of striking and durable clinical responses in some patients with metastatic disease and a reasonable response rate in many tumour types. The activity of checkpoint blockade immunotherapy is not restricted to melanoma or lung cancer, and additional indications are expected in the future, with responses already reported in renal cancer, bladder cancer, and Hodgkin's lymphoma among many others. Additionally, the interactions between radiation and the immune system have been investigated, with several studies describing the synergistic effects on local and distant tumour control when radiation therapy is combined with immunotherapy. Clinical enthusiasm for this approach is strengthened by the many ongoing trials combining immunotherapy with definitive and palliative radiation. Herein, we discuss the biological and mechanistic rationale behind combining radiation with checkpoint blockade immunotherapy, with a focus on the preclinical data supporting this potentially synergistic combination. We explore potential hypotheses and important considerations for clinical trial designs. Finally, we reintroduce the notion of radiosensitising immunotherapy, akin to radiosensitising chemotherapy, as a potential definitive therapeutic modality.

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Introduction

Radiation therapy has a long history in the specialty of oncology and is effective in treating unresected disease and preventing locoregional recurrence after surgery.[1] Historically, larger treatment areas were needed because of limitations in treatment planning, imaging, and radiation delivery systems. With the use of large radiation fields encompassing substantial volumes of bone marrow, pronounced reductions in blood counts were seen, thus reinforcing the notion that radiation is generally immunosuppressive.[2] However, with the advent of advanced radiation therapy planning and delivery, including highly focused radiation techniques, the ability to treat tumours has undergone a remarkable transformation. Stereotactic radiosurgery and stereotactic ablative radiotherapy (also termed stereotactic body radiation therapy [SBRT]) enable the delivery of radiation therapy with millimetre precision and can minimise dose to surrounding tissue structures, including bone marrow.[3] Image-guided intensity-modulated radiation therapy has furthered these advancements, substantially reducing radiation treatment fields and allowing a higher tumoricidal dose to be used.[4] This fundamental change necessitates a re-examination of the immunological effects of modern radiation treatment.

Radiation is widely known to induce tumour cell death through DNA damage. However, several studies have suggested that the immune system has an important role in the therapeutic effects of radiation, promoting tumour cell death in the radiation field. Some of the earliest data to implicate the immune system in the therapeutic effects of radiation were reported by Stone and colleagues,[5] who treated chemically induced fibrosarcomas with various doses of radiation and calculated the dose needed to control 50% of tumours. When they stimulated the immune system with a crude bacterial preparation, the dose of radiation needed to control the tumours was notably reduced.[5] Conversely, when animals were immunosuppressed before treatment either by whole-body radiation or thymectomy, a much higher dose of radiation was needed to control tumour growth. These data suggest that beyond the traditional effects of radiation as a DNA-damaging agent, the host immune system can affect therapeutic efficacy of radiation. How the radiation and immune system interacted was unclear; however, this effect was examined further in other studies and the subsets of immune cells that might be needed were delineated, most important of which seemed to be the CD8 T cells.[6–9] Taken together, available data suggest that cells of the immune system have a key role in tumour cell death within the radiation field. In view of these interactions, combining radiation with checkpoint blockade immunotherapy could increase radiosensitisation and improve local tumour control. Thus, we will use the term radiosensitising immunotherapy throughout this Review to emphasise this interaction and to emphasise similarities to the use of traditional chemotherapy as agents that augment the clinical effects of radiation therapy.[10,11]

Several new and important advancements have been made in immunotherapy,[12,13] including adoptive T-cell transfer, dendritic cell vaccines, peptide vaccines, oncolytic viruses, cytokine therapy, agonist monoclonal antibodies, antagonist monoclonal antibodies, and small molecules. Of these new advances, checkpoint blockade immunotherapy is one of the most exciting forms of immunotherapy treatment. The body of clinical data investigating the activity of checkpoint blockade immunotherapy is established and growing,[14–20] and additional US Food and Drug Administration-approved indications for different disease sites are expected. However, the efficacy and mechanism of action of checkpoint blockade immunotherapy dictates a change in thinking regarding the successes and failures of immunotherapy over the past two decades. The simple analogy that bears repeating is that of driving a car: for

years immunological approaches were focused on stepping on the accelerator without realising that the brakes were engaged; figuratively spinning the wheels without widespread clinical success. Arguably, the immune system has more powerful brakes than accelerators, and tumour cells engage powerful negative feedback loops that usually function to maintain homoeostasis and prevent autoimmunity. Thus, for any increase in positive stimulus, the immune system might apply a greater negative stimulus to counteract this activity. Clinically, the existence of these systems raises the question as to the threshold or level of activation that is needed to break self-tolerance. Furthermore, the clinical effectiveness of checkpoint blockade immunotherapy challenges the belief that functional cytotoxic T cells are deleted or not present in patients with advanced tumours. Indeed, the clinical activity of checkpoint blockade immunotherapy clearly shows that anti-tumour T cells remain present but are tolerised or anergised, and can be reactivated or reprogrammed by the appropriate stimulus. These fundamental questions herald a change in thinking, as immunotherapy establishes itself as the fourth pillar of cancer treatment alongside surgery, chemotherapy, and radiation therapy. Unfortunately, not all patients respond to single-agent or dual-agent checkpoint blockade, and the activity of existing agents may be restricted to specific disease types. Therefore, new studies are needed to establish and improve the responses reported. As with conventional chemotherapy, combinatorial therapies pairing checkpoint blockade immunotherapy with chemotherapy, targeted therapies, surgery, or radiation therapy represent the next logical step.

With regard to combining radiation and immunotherapy, two distinct clinical questions need to be addressed: can adding immunotherapy to definitive radiation (radiosensitising immunotherapy) contribute to improvements in locoregional control; and can adding radiation to immunotherapy contribute to enhanced distant or systemic disease control via radiation-induced immune responses or the abscopal effect?[21] Addressing these two very different questions will necessitate unique strategies and approaches. Many tumour types that have been successfully treated with radiosensitising chemotherapy have been chosen to investigate radiosensitising immunotherapy. These include: high-grade glioma (radiosensitising temozolomide), head and neck cancers (radiosensitising cisplatin), lung cancer, gastrointestinal malignancies including colorectal cancer (radiosensitising fluorouracil), gynaecological malignancies (radiosensitising cisplatin), and bladder cancer (radiosensitising cisplatin). Additionally, stereotactic radiosurgery or SBRT might be well suited for investigation of concurrent checkpoint blockade immunotherapy since concurrent chemotherapy is usually not given during SBRT (eg, in early-stage lung cancer, brain metastases, pancreatic cancer, and prostate cancer). Herein, the biological and mechanistic rationale behind combining radiation with checkpoint blockade immunotherapy is discussed with a focus on preclinical data supporting this combination in many disease sites. We will first consider the immunological effects of radiation alone before distinguishing between the effects of radiation combined with checkpoint blockade immunotherapy on local control (radiosensitising immunotherapy) versus systemic or distant control (abscopal effect).

Immunological effects of radiation as a monotherapy

Radiation enhances MHC class I surface expression, calreticulin expression, and release of HMGB1

MHC class I molecules have been described as "the window into the cell" and present intracellular antigenic peptides of eight to nine aminoacids that can be recognised by CD8 T cells.[22] One of the best-studied mechanisms by which radiation can enhance immune responses or the efficacy of immunotherapy is the upregulation of MHC class I.[6,23–26] Since many tumours downregulate MHC expression as a mechanism to evade detection by the immune system, this upregulation is an important component of the immune response. This process of immune evasion is similar to that used by several viruses, which encode genes that interfere with MHC class I expression and the peptide-loading pathway to escape detection by the immune system and establish latency. Although the absence of MHC class I could be detected by other cytotoxic immune-cell populations including natural killer cells, the loss of MHC class I enables tumour cells to go unrecognised by alpha-beta CD8 T cells, which form the major cell-mediated cytotoxic arm of the adaptive immune system.

Many studies have investigated the changes in MHC class I expression and antigen presentation that occur after radiation.[23–25,27] Reits and colleagues[24] showed that radiation upregulates MHC class I expression in a dose-responsive manner in both tumour cells and irradiated kidneys in vitro and in vivo. Mechanistically, this upregulation seemed to be mediated by radiation-induced activation of mTOR, and subsequent enhanced translation and antigen presentation.[24] An independent group confirmed that the mTOR pathway could be crucial in radiation-induced immune responses.[28] In studies by Hodge and colleagues,[29] radiation induced a substantial increase in the release of HMGB1 and enhanced surface expression of calreticulin in human prostate, breast, and lung cell lines. HMGB1 is a chromatin-binding protein and nuclear transcription factor. However, when HMGB1 is released extracellularly from inflammatory or dying cells, it functions as a damage-associated molecular pattern, a potent proinflammatory mediator, and activates dendritic cells, most likely by binding to Toll-like receptor 4.[30,31] Calreticulin is a lectin and molecular chaperone for MHC peptide loading on the luminal surface of the