The future of radiotherapy and immunotherapy concomitantly in cancer management
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ABSTRACT
Immunotherapy is a developing field in cancer treatment. Immunotherapy using immune checkpoint inhibitors has been successful in treating patients with metastatic disease, as well as patients who are refractory to standard treatments. Although immunotherapy has yielded considerably positive outcomes, its clinical benefits are limited to a small subset of patients. A combination of radiotherapy and immunotherapy has been shown to provide greater clinical benefits to more patients. Radiation, particularly hypofractionated radiation with stereotactic radiosurgery or stereotactic body radiotherapy, works by priming T cells, upregulating pro-inflammatory chemokines, and increasing the immunogenicity of tumor cells. Tumor cells develop immunosuppressive mechanisms that protect them from attack by the immune system. Immunotherapy works by disrupting the ability of tumor cells to setup these defenses. When combined with radiotherapy, it can synergistically enhance tumor cell death via cytotoxic T cells, thus causing systemic tumor regression and generating better clinical response.

KEYWORDS cancer, immunotherapy, radiation therapy, radioimmunotherapy, radiotherapy, tumor

Over the past few decades, radiotherapy has been used to treat various forms of cancers. The average success rate of radiotherapy has increased over time due to technological advances. In particular, the development of radiation therapy techniques, such as intensity-modulated radiation therapy, image-guided radiation therapy, ablative stereotactic radiosurgery (SRS), and stereotactic body radiotherapy (SBRT) have been significant. Apart from radiotherapy, there have been advances in other cancer treatment modalities. However, mortality and morbidity from cancers are still high, especially for those in advanced stages. Newer cancer treatment modalities continue to emerge and develop, including nanotechnology cancer therapy and immunotherapy. Immunotherapy modalities for cancer treatment include immune checkpoint inhibitors, adoptive cell transfer therapy, and oncolytic virus therapy. Currently, the most widely used modalities in clinic are immune checkpoint inhibitors such as programmed cell death protein-1
(PD-1) inhibitors, programmed death ligand 1 (PD-L1) inhibitors, and cytotoxic T-lymphocyte associated protein-4 (CTLA-4) inhibitors. In the rest of this article, immunotherapy will solely refer to the use of immune checkpoint inhibitors.

Several methods are being explored to maximize the benefits of immunotherapy. One method that has proved to be effective is the combination of radiotherapy and immunotherapy. Several clinical trials have reported benefits from the combination of radiotherapy and immunotherapy in the treatment of various solid tumors such as melanoma, non-small-cell lung cancer (NSCLC), cervical cancer, head and neck cancer, liver cancer, brain cancer, and prostate cancer.¹⁻³

Following reports of tangible results from this combination therapy, there is a drive to establish the effects of combination therapy in select populations, particularly patients who are refractory to standard treatments. This review was aimed to demonstrate the rationale behind combining radiotherapy and immunotherapy, but not intended to suggest nor recommend the use of this combination therapy in routine standard daily practice.

**Immune checkpoint inhibitors: current clinical use**

The immune system combats potentially harmful foreign antigens such as bacteria, viruses, and fungi. A key component of the immune system function is its ability to discriminate between self and non-self molecules, through immune tolerance and variety of regulatory cells and mechanisms that suppress autoimmune reactivity. There are physiological mechanisms through which immune cell over-reactivity is counteracted in the body. However, these mechanisms can be hijacked and employed by tumors to escape immune attacks. Several well-known immune inhibitory pathways are known to be associated with the ability of tumors to escape immune recognition. They include the CTLA-4 and PD-1 pathways.

Cytotoxic T-lymphocyte associated protein-4 (CTLA-4), a transmembrane protein found in T cells, functions as an immune inhibitory signal.⁴ Programmed cell death protein-1 (PD-1) is a receptor found in various immune cells. Programmed death ligand 1 (PD-L1) is found in many tumor cells.⁵ The binding of PD-1 to its ligand PD-L1 results in an inhibitory immune signal. Several antibodies have been devised to target those receptors, with varying levels of success.

Several monoclonal antibodies targeted against CTLA-4, PD-1, and PD-L1 have been approved by United State Food and Drug Administration (USFDA) approval for clinical use. Ipilimumab, an anti-CTLA-4, was the first USFDA-approved checkpoint inhibitor. Studies have shown it increases survival in metastatic melanoma.⁶,⁷ Pembrolizumab, a humanized monoclonal antibody of PD-1, has been approved and used to treat melanoma, NSCLS, and advanced squamous cell carcinoma of head and neck.⁸⁻¹⁰ Nivolumab, a humanized monoclonal antibody of PD-1, has also been approved and used for melanoma, NSCLS, renal cell cancer, and relapsed Hodgkin lymphoma.¹¹⁻¹³

Although using these immune checkpoint inhibitors has resulted in increased survival rates, the beneficial effects have been restricted to a small subset of patients. Two major randomized controlled trial, which led to the approval of ipilimumab for treatment in advanced melanoma, showed a response rate of only 10–15%.⁶,⁷ A different melanoma trial randomized patients between pembrolizumab and chemotherapeutic agent of investigator’s choice. Results from this study showed that patients on pembrolizumab had a significantly higher progression-free survival rate at 9 months of 29% versus 8% in patients on standard chemotherapy.¹⁰ In a nivolumab trial, melanoma patients who received nivolumab showed an overall response rate of 40% compared to 13.9% in patients treated with dacarbazine.¹⁴

The restriction in therapeutic benefits of immunotherapy to a subgroup of patients is likely because not all tumors are adequately infiltrated by T cells.¹⁵ It has been demonstrated in preclinical models that the presence of T cells in the tumor microenvironment is required for the efficacy of immune checkpoint inhibitors.⁴ To ensure the effective application of therapeutic resources, molecular tests are being developed to accurately predict patients that would benefit from immunotherapy.

Furthermore, increasing the benefit of immunotherapy in cancer patients is a focus of research. One way to achieve this is by combining multiple immune checkpoint inhibitors. In a trial conducted in metastatic melanoma patients, the patients were randomized into separate groups in which patients either received a combination of nivolumab-ipilimumab or a monotherapy of either
Apart from the immunosuppression induced by tumor cells, radiation can also be immunosuppressive. As lymphocytes are very sensitive to radiation, standard radiation treatment with conventional doses, large treatment volume (to control gross tumor, potential clinical spread, and drain lymph nodes) and protracted treatment duration can induce lymphopenia. Lymphopenia has been linked with decreased survival.²⁴

However, radiation-induced lymphopenia is uncommon in hypofractionated radiation with either the SRS or SBRT technique.²⁵ In SRS or SBRT, there is a smaller target volume, a higher dose to target, but a lower dose to normal tissue limited to less than 6 fractions. Therefore, radiation-induced lymphocyte death using the SRS or SRBT technique is much lower than what is observed in conventional radiation. This may explain why the abscopal effect is only observed in hypofractionated radiation at a dosage between 6–8 Gy per fraction, at a frequency of 5–6 fractions daily.

Combining radiotherapy and immunotherapy (radioimmunotherapy): theoretical concept to proof of concept

The use of radiation to prime intra-tumoral T cells combined with immunotherapy to counteract the immunosuppressive pathways elicited by tumor cells is theoretically plausible. Radiotherapy is an effective and relatively cheap modality to increase tumor immunogenicity. When coupled with immunotherapy, an increase in cytotoxic T cell-induced tumor cell death is expected. The mechanism is described in Figure 1.

Multiple preclinical studies have validated the effects of radioimmunotherapy.²⁶⁻²⁸ A combination of radiation and the injection of dendritic cells in a mice model showed a significant increase in tumor cell death than was observed when either radiation or administration of dendritic cells was administered alone.²⁶ In another experiment conducted in the mice model, radioimmunotherapy proved effective for the target lesion, as well as for distant non-target lesions.²⁷ Furthermore, the radiation resulted in an upregulation of PD-L1 in the tumor microenvironment,²⁸ confirming the therapeutic benefits of radioimmunotherapy.

To achieve optimal tumor regression, the right sequence of the combination must be used. Furthermore, the appropriate radiation technique, the target lesions, and effective dose selection

nivolumab alone or ipilimumab alone. There was a significantly higher rate of complete response among patients on nivolumab-ipilimumab combination therapy (8.9%) compared to the rate in patients treated by either nivolumab alone or ipilimumab alone (2.2%).¹⁷ Although this study yielded significant results, a combination of immune checkpoint inhibitors still appears to be beneficial in a select subgroup of patients. Another potential way to increase therapeutic range is to combine immunotherapy with radiotherapy. Mechanistic and clinical evidence for the use of this form of combination therapy will be discussed in the following sections.

Hypofractionated radiotherapy: local control and the abscopal effect

Radiotherapy is a form of standard treatment for cancer. Radiotherapy has been widely used across the world for decades to control local and regional tumors, with conventional doses between 1.8 Gy and 2 Gy per fraction. With advances in technology and the delivery techniques for radiotherapy, higher doses are being attempted to target tumors without jeopardizing normal organ function. This has been achieved mainly through the SRS and SBRT techniques, which are aimed at improving local tumor control. As more SRSs and SBRTs are being performed in clinic, occasional regression of non-target tumor lesions located outside of the radiation field have been documented.¹⁸ This phenomenon is called the abscopal effect.

The abscopal effect observed in radiotherapy is known to be mediated by T cells.²⁹ Radiation has been shown to induce the release of pro-inflammatory chemokines that facilitate T cell migration into tumors.³⁰ Furthermore, radiation induces upregulation of the major histocompatibility complex class I (MHC class I),³¹ and increases the probability of presenting the tumor antigen to cytotoxic T cells. Therefore, radiation increases the probability that tumor cells are killed by cytotoxic T cells.³²

Radiation alone rarely results in the abscopal effect. Radiation primes antitumor T cells. However, tumors can escape immune destruction by activating immunosuppressive mechanisms such as upregulating PD-L1 in tumor cells, inducing PD-1 expression in intra-tumoral T cells, and expression of transforming growth factor beta (TGFβ) (a potent immunosuppression signal).³³
must be established. Multiple clinical trials are being conducted to determine the best combination regimen in various forms of tumors. Given its success in preclinical studies, radioimmunotherapy is now being studied in multiple clinical trials. Data from published and ongoing phase I/II studies have been encouraging. Several phase III clinical trials into radioimmunotherapy are underway including in NSCLC (clinicaltrials.gov: NCT02768558), head and neck cancer (clinicaltrials.gov: NCT03040999), and glioblastoma (clinicaltrials.gov: NCT02617589). Result of the studies will be available in near future and may provide new treatment options for cancer treatment.

While radioimmunotherapy is a promising potential therapy, substantial clinical benefit in many forms of cancers is yet to be confirmed in ongoing phase III clinical trials. Furthermore, the best sequence of radiation and immunotherapy is yet to be determined in clinical trials. Questions regarding tumor histology, lesions to be irradiated, number of fractions, dose of radiation, patient’s immune status, performance status, and prior treatments are all important aspects of combination therapy that currently being investigated.

**Conclusions**

The evolution of immunotherapy as a form of cancer treatment has been significant, especially in patients with metastatic or cancers that have been refractory to standard treatments. Immunotherapy continues to produce a positive clinical response. However, its therapeutic benefits are limited to a small subset of patients.

Expanding the patient pool that can benefit from immunotherapy has been a target for research. An effective way of increasing this pool is by combining radiotherapy and immunotherapy. Radiotherapy, using SRS or SBRT, works by priming the T cells and upregulating various pro-inflammatory chemokines to enhance immunogenicity. Immunotherapy blocks the immunosuppressive pathways that are utilized by tumor cells. In concert, radioimmunotherapy results in enhanced cytotoxic T cell-mediated tumor cell death. Therefore, clinical response is amplified, and patients unresponsive to monotherapy are more likely to receive therapeutic benefits from radioimmunotherapy.

Understanding the basic rationale for combining radiotherapy and immunotherapy will provide a mechanistic approach to clinicians and researchers.
for its application. Data from future studies will provide better guidance for the clinical use of radioimmunotherapy.

Conflict of Interest
The authors affirm no conflict of interest in this study.

Acknowledgment
The authors would like to thank dr. IGAA Jayanthi Wulan, which has helped in designing the figure and illustrating synergistic mechanism of radiotherapy and immunotherapy presented in this article.

Funding Sources
None.

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Medical Journal of Indonesia