Review Article

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 programed 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] Programed 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.[16] 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

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.[19] Radiation has been shown to induce the release of pro-inflammatory chemokines that facilitate T cell migration into tumors.[20] Furthermore, radiation induces upregulation of the major histocompatibility complex class I (MHC class I),[21] 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.[22]

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).[23]

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

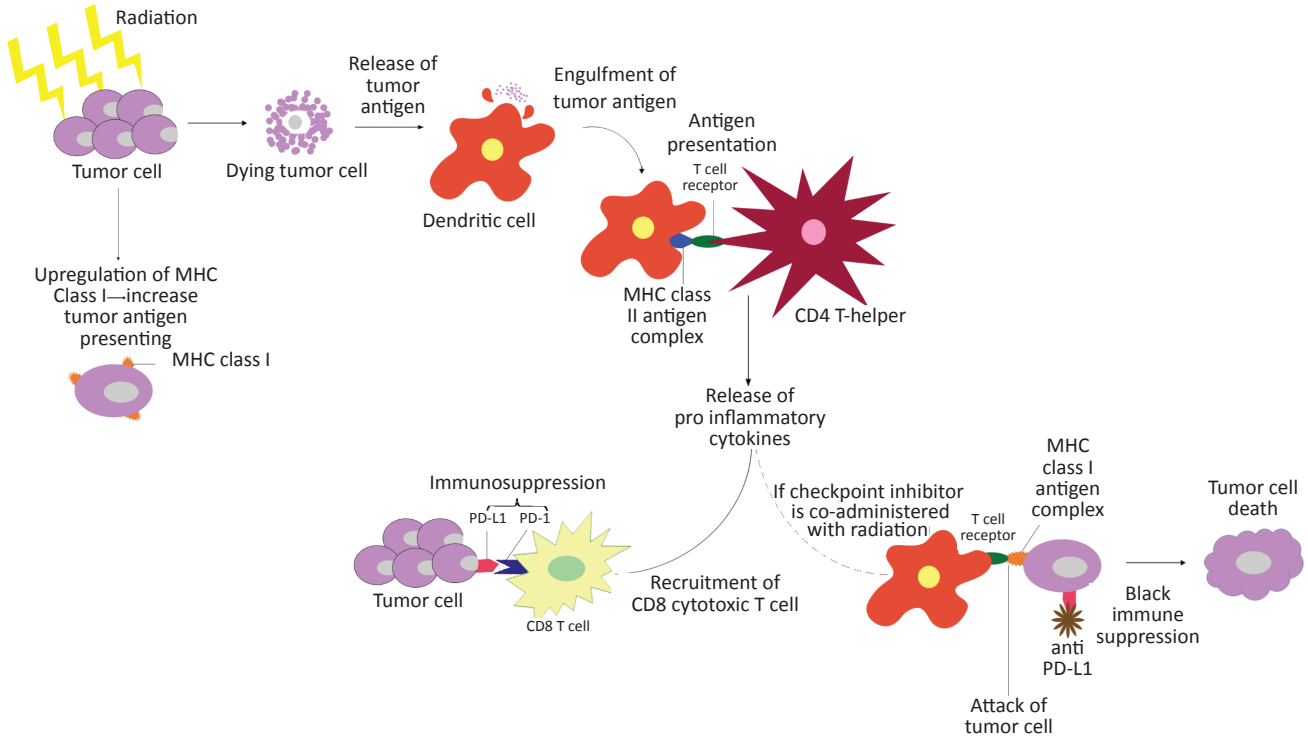

Figure 1. Synergistic effect of combining radiotherapy and immunotherapy. Radiotherapy will act to increase tumor antigen, which increases tumor antigen presentation. A combination of immunotherapy counteracts immune escape by tumor cells via the PD-1/PD-L1 mechanism (when immunotherapy is co-administered with radiotherapy – dashed line). Therefore, the probability of tumor cell death is increased. MHC=major histocompatibility complex; PD-1=programed cell death protein-1; PD-L1=programmed death ligand 1

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.[1,29,30] 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.

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REFERENCES

1. Kang J, Demaria S, Formenti S. Current clinical trials testing the combination of immunotherapy with radiotherapy. J Immunother Cancer. 2016;4:51.
2. Kwon ED, Drake CG, Scher HI, Fizazi K, Bossi A, van den Eertwegh AJ, et al. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol. 2014;15(7):700–12.
3. Hiniker SM, Reddy SA, Maecker HT, Subrahmanyam PB, Rosenberg-Hasson Y, Swetter SM, et al. A prospective clinical trial combining radiation therapy with systemic immunotherapy in metastatic melanoma. Int J Radiat Oncol Biol Phys. 2016;96(3):578–88.
4. Walunas TL, Bakker CY, Bluestone JA. CTLA-4 ligation blocks CD28-dependent T cell activation. J Exp Med. 1996;183(6):2541–50.
5. Speiser DE, Ho PC, Verdeil G. Regulatory circuits of T cell function in cancer. Nat Rev Immunol. 2016;16(10):599–611.
6. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363(8):711–23.
7. Robert C, Thomas L, Bondarenko I, O'Day S, Weber J, Garbe C, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med. 2011;364:2517–26.
8. Pai-Scherf L, Blumenthal GM, Li H, Subramaniam S, Mishra-Kalyani PS, He K, et al. FDA approval summary: pembrolizumab for treatment of metastatic non-small cell lung cancer: first-line therapy and beyond. Oncologist. 2017;22(11):1392–9.
9. Chow LQM, Haddad R, Gupta S, Mahipal A, Mehra R, Tahara M, et al. Antitumor activity of pembrolizumab in biomarker-unselected patients with recurrent and/or metastatic head and neck squamous cell carcinoma: results from the phase Ib KEYNOTE-012 expansion cohort. J Clin Oncol. 2016;34(32):3838–45.
10. Ribas A, Puzanov I, Dummer R, Schadendorf D, Hamid O, Robert C, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. Lancet Oncol. 2015;16(8):908–18.
11. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus docetaxel in advanced squamous-cell non–small-cell lung cancer. N Engl J Med. 2015;373:123–35.
12. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med. 2015;373:1803–13.
13. Younes A, Santoro A, Shipp M, Zinzani PL, Timmerman JM, Ansell S, et al. Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial. Lancet Oncol. 2016;17(9):1283–94.
14. Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015;372:320–30.
15. Gajewski TF. The next hurdle in cancer immunotherapy: overcoming the non-T-cell-inflamed tumor microenvironment. Semin Oncol. 2016;42(4): 663–71.
16. Spranger S, Koblish HK, Horton B, Scherle PA, Newton R, Gajewski TF. Mechanism of tumor rejection with doublets of CTLA-4, PD-1/PD-L1, or IDO blockade involves restored IL-2 production and proliferation of $CD8^+$ T cells directly within the tumor microenvironment. J Immunother Cancer. 2014;2:3.
17. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med. 2015;373:23–34.
18. Abuodeh Y, Venkat P, Kim S. Systematic review of case reports on the abscopal effect. Curr Probl Cancer. 2016;40(1):25–37.
19. Demaria S, Ng B, Devitt ML, Babb JS, Kawashima N, Liebes L, et al. Ionizing radiation inhibition of distant untreated tumors (abscopal effect) is immune mediated. Int J Radiat Oncol Biol Phys. 2004;58(3):862–70.
20. Matsumura S, Demaria S. Up-regulation of the pro-inflammatory chemokine CXCL16 is a common response of tumor cells to ionizing radiation. Radiat Res. 2010;173(4):418–25.
21. Reits EA, Hodge JW, Herberts CA, Groothuis TA, Chakraborty M, Wansley EK, et al. Radiation modulates the peptide repertoire, enhances MHC class I expression, and induces successful antitumor immunotherapy. J Exp Med. 2006;203(5):1259–71.
22. Garnett CT, Palena C, Chakarborty M, Tsang KY, Schlom J, Hodge JW. Sublethal irradiation of human tumor cells modulates phenotype resulting in enhanced killing by cytotoxic T lymphocytes. Cancer Res. 2004;64(21):7985–94.
23. Vanpouille-Box C, Diamond JM, Pilones KA, Zavadil J, James JS, Formenti SC, et al. TGFβ is a master regulator of radiation therapy-induced anti- tumor immunity. Cancer Res. 2015;75(11):2232–42.
24. Yovino S, Kleinberg L, Grossman SA, Narayanan M, Ford E. The etiology of treatment-related lymphopenia in patients with malignant gliomas: modeling radiation dose to circulating lymphocytes explains clinical observations and suggests methods of modifying the impact of radiation on immune cells. Cancer Invest. 2013;31(2):140–4.
25. Wild AT, Herman JM, Dholakia AS, Moningi S, Lu Y, Rosati LM, et al. Lymphocyte-sparing effect of stereotactic body radiation therapy in patients with unresectable pancreatic cancer. Int J Radiat Oncol Biol Phys. 2016;94(3):571–9.
26. Nikitina EY, Gabrilovich DI. Combination of gamma-irradiation and dendritic cell administration induces a potent antitumor response in tumor-bearing mice: approach to treatment of advanced stage cancer. Int J cancer. 2001;94(6):825–33.
27. Dewan MZ, Galloway AE, Kawashima N, Dewyngaert JK, Babb JS, Formenti SC, et al. Fractionated but not single dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody. Clin Cancer Res. 2009;15(17):5379–88.
28. Deng L, Liang H, Burnette B, Beckett M, Darga T, Weichselbaum RR, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. J Clin Invest. 2014;124(2):687–95.
29. Seung SK, Curti BD, Crittenden M, Walker E, Coffey T, Siebert JC, et al. Phase 1 study of stereotactic body radiotherapy and interleukin-2–tumor and immunological responses. Sci Transl Med. 2012;4(137):137ra74.
30. Tang C, Welsh JW, de Groot P, Massarelli E, Chang JY, Hess KR, et al. Ipilimumab with stereotactic ablative radiation therapy: phase I results and immunologic correlates from peripheral T-cells. Clin Cancer Res. 2017;23(6):1388–96.