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Mini Review

An Innovative Approach to Multimodal Cancer Treatment: Combining Radiotherapy and Immunotherapy

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Abstract

Immunotherapy is a promising modality of cancer treatment that has shown encouraging results in patients with a variety of tumor types, most notably in metastatic melanoma. durable responses seen in a minority of patients are impressive, and have led to the search for adjunctive therapies to increase response rates. Radiotherapy is capable of inciting inflammation and increasing T cell infiltration in tumors, making it an attractive candidate for combination therapy. The synergy between radiotherapy and immunotherapy has been described for checkpoint inhibitors in a small number of patients. Furthermore, total body irradiation has been used in adoptive cell transfer protocols with improved outcomes. While these therapies are in the early stages of clinical application, definitive studies are needed to clarify the role of combining radiotherapy with immunotherapy. We review the current evidence for these combinations and highlight ongoing studies of these multimodal approaches to cancer therapy.

Introduction

The combination of immunotherapy and radiotherapy is a promising paradigm in cancer treatment. Melanoma is a particularly immunogenic tumor, and as such is the most extensively studied in this realm. We review the potential for combining radiotherapy with immune checkpoint inhibition and adoptive cell transfer, both of which are emerging treatments for metastatic melanoma.

Radiotherapy and Checkpoint Inhibition

Immune modulating agents have been used for decades as a treatment modality in melanoma albeit with limited success until recently. Adjuvant interferon produces a 4% benefit in overall survival [1] whilst high dose IL-2 in metastatic melanoma can produce a minority (4%) of durable responses lasting a number of years [2]. The development of CTLA-4 and anti-PD1/PDL1 immune checkpoint inhibitors has significantly improved outcomes in metastatic disease [3-5], and has ushered in an exciting new era of melanoma treatment and immune therapy of cancer. Ipilimumab, a monoclonal antibody that blocks CTLA-4, a key negative regulator of T cell immune responses, was the first FDA-approved immune checkpoint inhibitor for the treatment of unrespectable and metastatic melanoma. Durable responses three years after ipilimumab treatment as part of a clinical trial or the Expanded Access Programmed (EAP) have been shown in 22% of patients; while two year survival post treatment [6] with an anti-PD1 inhibitor is approximately 40% [5].

The two pivotal trials that demonstrated improved survival with ipilimumab treatment were in patients with cutaneous melanoma [3, 4]. The subsequent expanded access program allowed treatment of mucosal and uveal melanomas. Outcomes in mucosal melanomas appeared to be similar to cutaneous [7], and whilst poorer responses and outcomes were seen in uveal melanomas there was demonstration of activity [8]. Despite encouraging results for melanoma and other cancers, the majority of patients treated with immune checkpoint inhibitors fail to respond, and mechanisms of resistance are poorly defined. Impaired antigen presentation, energy, poor T-cell infiltration, an immunosuppressive microenvironment, and expression of alternative immune checkpoint receptors may impair responses. Strategies to overcome resistance are likely to involve combinations of agents such as CTLA-4 and PD-1 checkpoint inhibitors or treatment modalities including radiotherapy.

Radiotherapy causes irreparable DNA damage, exerting a cytotoxic effect that is often accompanied by an acute inflammatory reaction. Fractionation of radiotherapy allows for normal tissue recovery, as well as tumour cell reoxygenation between doses to prevent hypoxia driven resistance [9]. Radiation has been shown in preclinical models to enhance natural killer cell activity [10] and increase CD8+ and CD4+ tumour infiltration in irradiated lesions, both of which may be increased with optimal fractionation [11]. Increased antigen release and epitope spreading via an initial cytotoxic effect may further promote an immune response [12]. The abscopal effect describes the phenomenon whereby tumor responses are seen post-radiation at sites distant from the irradiated lesion [13]. The mechanism is thought to be immune-mediated [14]. Abscopal effects have been described when radiation was combined with interferon, IL-2 and ipilimumab, although the mechanism of action with each agent may differ. Early phase trials combining radiotherapy with either interferon [15] or IL-2 [16] have suggested that these combinations are safe, but improvement in outcomes has yet to be demonstrated. A retrospective review of 29 patients at Memorial Sloan Kettering Cancer Centre noted no significant increase in adverse events with the combination of ipilimumab and radiotherapy; however at the highest doses of radiation, there were increased radiation-related toxicities [17]. The optimal scheduling of radiotherapy, single dose

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vs hypo/hyper fractionation, target volume, and dose of radiotherapy is yet to be determined. It is also unclear whether the optimal effect would occur with radiotherapy given in combination or in sequence with immunotherapy.

Case reports of abscopal effects with ipilimumab were originally described in patients receiving radiotherapy post-ipilimumab failure who had no further treatment options [17]. While hyper-fractionated radiation courses over several weeks have dominant immunosuppressive effects, preclinical models have shown an increase in immune infiltrates with hypofractinated courses. The optimal schedule is yet to be defined. For example in a mouse model, CD8+ infiltration and enhanced natural killer cell activity was seen when ipilimumab was combined with radiotherapy, but was superior with fractionated dosing compared to a single high dose [18]. Combining these two modalities would therefore seek to either produce a synergistic effect or stimulate a greater stimulatory immune response to promote tolerance or elimination of tumour.

Ongoing trials combining radiotherapy and ipilimumab vary in design. While the standard dose of ipilimumab is 3mg/kg for 4 doses, an increased rate of responses (and toxicity) may be seen with 10mg/kg. This does is also under evaluation. Three trials aim to evaluate ipilimumab at 3mg/kg in combination with radiotherapy to a metastatic lesion. Ipilimumab in combination with radiotherapy starting 2 days after cycle 1 is being evaluated in the NCT01449279 single arm study. NCT01689974 is a randomized trial of ipilimumab plus or minus radiotherapy which is given 30Gy in 5 fractions over a week starting 3 days after commencing ipilimumab, and the Radvax trial (NCT01497808) uses stereotactic radiotherapy in escalating fractions prior to the start of ipilimumab. The dose of 10mg/kg for four doses followed by maintenance every 12 weeks in combination with escalating doses of radiotherapy (9-24 Gy in 3 fractions, delivered between cycle 2 and 4 of ipilimumab) is the subject of trials NCT01557114 and NCT01565837, although the latter delivers stereotactic radiotherapy between the first and third doses of ipilimumab. NCT01703507 randomizes patients between whole brain radiotherapy (WBRT) and stereotactic brain radiosurgery (SRS) and escalating doses of ipilimumab given every three weeks for 4 doses starting either during the first 2 weeks (WBRT) of radiotherapy or on the same day (SRS) of radiotherapy treatment. The NCT01769222 study utilizes intralesional cutaneous ipilimumab in escalating doses with radiotherapy delivered in 3 fractions beginning within 48 hours of commencing ipilimumab.

The possibility of promoting a more stimulatory immune environment with the use of radiotherapy is being explored in NCT01730157 in which ipilimumab is given 4 weeks after hepatic embolization with yittrium (90) microspheres in metastatic (to the liver) uveal melanoma patients. Other trials seeking to explore the effect of radiotherapy with other immunomodulators include a trial of radiotherapy to skin lesions followed by peri-tumoural dendritic cell injection and interferon injections (NCT00278018), a phase II trial randomizing to either high dose IL-2 alone or with stereotactic radiotherapy (20 Gy in 1 fraction or 40 Gy in 2 fractions) 3-5 days prior to IL-2 therapy (NCT01416831), and a phase II study of boost radiotherapy at 6-12 Gy to 1-5 metastatic fields in melanoma or renal cell carcinoma prior to high dose IL-2 (NCT01884961).

Radiotherapy and Adoptive Cell Transfer

Adoptive immunotherapy is an additional approach to immune therapy where anti-tumor effector immune cells are extracted from a patient's tumor or peripheral blood, prepared *in vitro*, and then reinfused. This approach has the advantage of facilitating the optimal delivery of essential signals to selected populations of effector cells, without the suppressive factors that exist in patients. Adoptive Cell Transfer (ACT) with Tumor-Infiltrating Lymphocytes (TIL) for metastatic melanoma has shown promising high response rates and durable responses in selected patients [19]. ACT involves generating a highly specific, potent immune response using autologous TILs extracted from a patient's metastatic lesion. Total Body Irradiation (TBI) has been used with high rates of success as an adjunct to the preparative lymphodepletion that is necessary prior to ACT for optimal clinical activity. ACT is currently limited to a select number of academic centers in the world due to its complexities and equipment required. A typical ACT protocol [19] involves harvesting tumor reactive T lymphocytes from the patient's resected metastatic tumor sample, culturing the cells ex-vivo, and subsequently selecting lymphocytes with superior growth and reactivity. These lymphocytes are then expanded ex-vivo using IL-2, and reinfused into the patient. In the shortest time frame, using a 'young' TIL protocol, TILs may be produced in 4 weeks [20]. In the interim, the patient receives a conditioning regimen of lymphodepletion which eliminates immune suppressor cells and results in increased availability of homeostatic cytokines to allow for better engraftment of the transferred TILs. After the TIL infusion, patients receive treatment with high dose IL-2, a T cell growth factor.

Various conditioning regimens have been tested, including cyclophosphamide 60mg/kg for two days with fludarabine 25mg/m^2 for five days, as well as the addition of myeloablation with total body irradiation requiring autologous stem cell rescue. Three sequential trials in metastatic melanoma patients using ACT with different preparatory regimens showed that chemotherapy alone had an objective response rate of 49%, adding 2 Gy of TBI had a response rate of 52%, while 12 Gy TBI resulted in a 72% objective response rate by RECIST criteria [21]. The responses were seen in all visceral sites, including the brain. Twenty of the 93 (22%) patients had complete tumor regression, and 19 have ongoing complete response beyond three years [19].

TBI is thought to improve outcomes by reducing regulatory T cell (Treg) reconstitution, thereby reducing the native immune suppression [22] and inducing a deeper lymphodepletion that increases the availability of homeostatic cytokines IL-7 and IL-15 [21]. Radiotherapy also activates the innate immune system, partly due to bacterial translocation from damage to the gut mucosa, which provides activating signals via toll-like receptors [23]. TBI is myeloablative, and autologous stem cell transplant with CD34+ cells is required. In the National Cancer Institute (NCI) study's 12 Gy protocol, patients receive 2 Gy twice daily starting on the last day of fludarabine treatment, for three consecutive days, and complete the radiation treatment one day before TIL infusion [21]. Mediastinal boost was given with protection to the lung area. In the 2 Gy protocol, patients received the entire radiation dose on the day after completing fludarabine, and received TIL infusion the day after TBI. Most patients recovered bone marrow function by 12-14 days, with

an average of 1-2 days delay for those in the higher radiation dose group. There were severe toxicities including one treatment-related death from neutropenic sepsis in a patient with previously existing but unrecognized diverticular abscess. The most common Grade 3-4 toxicities were febrile neutropenia, transfusion requirements of platelets and red blood cells, and thrombotic microangiopathy only in the 12 Gy TBI group.

To definitively determine the role of TBI in TIL therapy, investigators at the NCI are conducting an ongoing trial that randomizes patients receiving ACT with young TIL after lymphodepleting chemotherapy with cyclophosphamide and fludarabine, with or without 1200 cGy TBI in conjunction with autologous stem cell rescue (NCT01319565). A phase I/II trial of radiation and adoptive transfer in stage IV merkel cell carcinoma is recruiting (NCT01758458), as is a randomized controlled trial in esophageal cancer comparing radiotherapy alone versus radiotherapy plus DC-CIK (dendritc cell-cytokine induced killer cell) adoptive cell therapy (NCT01691664).

Taken together, preclinical and clinical reports of the benefit of radiotherapy in combination with immune modulating agents and adoptive cell transfer make this an attractive strategy to produce a synergistic effect and overcome resistance. Whether this can be applied broadly to other malignancies in addition to melanoma remains to be seen. The variability in immune responses and effect of these agents make it imperative to conduct translational research in tandem with clinical trials to help determine mechanisms of action and resistance, and to better guide treatment selection. The prospect of further optimizing patient outcomes is encouraging as we await the results of ongoing trials in this promising new era of cancer therapy.

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