

Teaching Case

4-1BB (CD137) and radiation therapy: A case report and literature review

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Introduction

Emerging immuno-oncology combination strategies include using radiation therapy (RT) with immunotherapeutic checkpoint blockade monoclonal antibodies (mAbs) such as CTLA-4 and PD-1 and represent a new and exciting strategy to improve outcomes in solid tumor malignancies.^{1,2} RT has the potential to augment immune responses,^{3,4} and cancer cells destroyed by RT are considered to be a source of tumor-associated antigens that can be processed by professional antigen-presenting cells.⁵

Because objective response rates using single checkpoint blockade with RT remains suboptimal, 1 strategy to improve outcomes has been to add costimulatory mAbs, such as 4-1BB.^{2,6} Expression of 4-1BB on antigen-presenting cells and T cells, in addition to its capacity to enhance effector function of activated T cells and promoting survival and expansion, has made it an

immunotherapy of interest for cancer treatment. Although immune checkpoint blockade in combination with radiation therapy for treatment of melanoma may potentially improve patient outcomes⁷ and potentiate an abscopal effect,⁸ it is unknown whether patients treated with combination radiation therapy and 4-1BB agonists will experience a similar result. 4-1BB has produced favorable responses in preclinical murine tumor models,^{6,9,10} but no clinical case studies have demonstrated the efficacy, safety, and response of combined therapy with 4-1BB agonists and radiation.

This report provides the first patient case of immune costimulatory directed therapy potentially augmented with RT. We describe the progression of disease despite several treatments with immunotherapy followed by excellent response to standard RT doses after treatment with 4-1BB.

Case Report

We describe the case of a 58-year-old male who initially presented with a nonhealing ulcer on the left posterior heel and was diagnosed with cutaneous malignant melanoma on punch biopsy in January 2012. A month later, he underwent wide local excision and sentinel lymph node biopsy with 2 positive nodes. He

Conflicts of interest: None.

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then underwent a laparoscopic groin dissection that was positive for 3 of 16 nodes and was started on adjuvant interferon therapy. After 8 months of treatment, a fine needle aspiration of a recurrent left groin node was positive for metastatic melanoma, and interferon therapy was discontinued because of disease progression. In April 2013, he underwent a left pelvic node dissection and had 2/11 positive nodes with extracapsular extension in a left inguinal node. His positron emission tomography/computed tomography scan was positive for other metastatic disease, and the patient started on vemurafenib therapy in August 2013. Because of disease progression, the patient was switched to dabrafenib and trametinib for approximately 1 year and then to 4 doses of ipilimumab and nivolumab from February 23 to April 27, 2015. Subsequently, the patient was treated with nivolumab as a single agent, which was stopped on September 18, 2015, because of progression.

Despite immunotherapy and BRAF inhibitor therapy, the patient's disease continued to progress and was started on a 41BB trial in December 2015. He was treated with the first cycle on December 17, 2015, and the second cycle on January 15, 2016. In February 2016, his disease continued to progress. The left adrenal lesion increased from 6.3 cm to 8.6 cm, the right conglomerate lymph node increased from 8.1 cm to 9.6 cm, the right inguinal lymph node decreased from 2.8 cm to 1.6 cm, and there was a new left gluteus lesion measuring 3.4 cm. Given the poor performance status (Eastern Cooperative Oncology Group [ECOG] 2) and extensive abdominal disease with failure to thrive, discussions included hospice and palliative RT. He elected for palliative radiation treatment,

receiving a dose of 30 Gy in 10 fractions from March 7 to March 29, 2016, to a growing large left pelvic mass and a right pelvic mass. He had excellent postradiation response and reported major improvement regarding his pain, an increase in overall performance status (ECOG 1), better ambulation, and increased well-being. The right pelvic mass initially measured 11×9.6 cm with encasement of the right ureter and right common iliac, external iliac, and internal iliac vessels (Fig 1A); a month after treatment, this measured 6.8×5.3 cm (Fig 1B, Table 1). Of note, this is not a typical response for bulky melanoma after RT. Gross tumor volume was defined as the mass, clinical target volume was an expansion of 0.5 cm from the gross tumor volume, and the planning target volume was an expansion of 0.5 cm from the clinical target volume. RT was delivered using a 6-MV energy source using the anteroposterior/posteroanterior technique. The dosimetry of this treated lesion is demonstrated in Fig 2A. At the end of the treatment, the patient experienced grade 1 nausea and grade 1 fatigue that improved by 1-month follow-up.

On May 3, the patient reported worsening symptoms, increased left lateral iliac pain, and ECOG 2. He then received additional palliative radiation from May 10 to May 23, 2016, to a left iliac wing soft-tissue mass and a 11.2×10.8 cm left adrenal mass (Fig 1C). He received 30 Gy \times 10 fractions, also with excellent response with left adrenal mass size reduction 6.7×5.4 cm of the (Fig 1D, Table 1) on follow-up computed tomography scan 1 month after treatment. Once again, this is an atypical response to RT for bulky melanoma. The dosimetry of the treated lesion in the left adrenal is demonstrated in Fig 2B. He tolerated the treatment well,

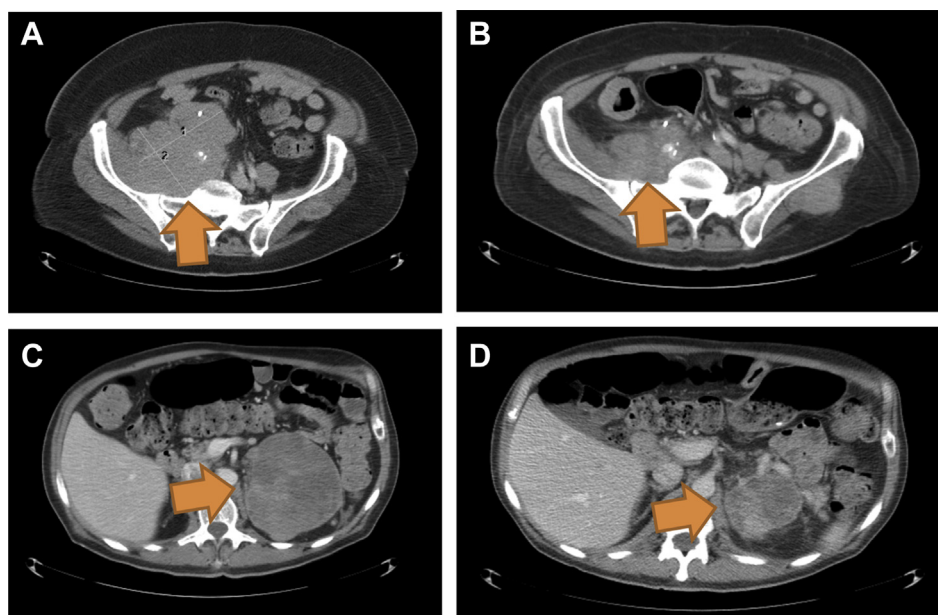


Figure 1 (A) Right psoas lesion initially measuring 11×9.6 cm. (B) Lesion demonstrated excellent response; at 1-month follow-up, lesion measured 6.8×5.3 cm. (C) Adrenal lesion originally measured 11.2×10.8 cm. (D) Lesion demonstrated excellent response at 10-month follow-up and measured 6.7×5.4 cm.

Table 1 Lesion sizes before and after radiation treatment

Location	Dose and fractionation	Lesion size on last scan before treatment (cm)	Dates treated	1-month follow-up size (cm)	3-month follow-up size (cm)
Lumbar spine/right pelvic mass	30 Gy/10 fractions	11.0 × 9.6	3/7/16-3/29/16	6.8 × 5.3	3.2 × 2.1
Left pelvis/femur	30 Gy/10 fractions	14.3 × 10.9	3/7/2016-3/29/16	3.9 × 2.6	3.2 × 2.6
Left adrenal	30 Gy/10 fractions	11.2 × 10.8	5/10/16-5/23/16	6.7 × 5.4	No imaging follow-up
Left iliac wing	30 Gy/10 fractions	5.3 × 3.3	5/10/16-5/23/16	2.1 × 1.4	No imaging follow-up
Left lateral thigh	30 Gy/10 fractions	15.0 × 8.5 (clinical examination)	6/29/16-7/13/16	NA	4.0 × 3.5

NA, not available.

only experiencing grade 1 fatigue from the end of treatment to 1-month follow-up (Table 1). Subsequently, the patient was treated palliatively to a 15.0 cm × 8.5 cm mass on clinical examination of the left thigh from June 29 to July 13, 2016. This mass was 4.0 cm × 3.5 cm at 3-month follow-up, and the patient experienced no toxicities from this treatment. Radiation treatment allowed

the patient to receive systemic therapy, improve localized pain, and improve performance status. The patient was last seen at our institution on October 24, 2016, and followed up at his home institution. Unfortunately, he had worsening of his symptoms and was ECOG 3 in November 2016. The patient has not followed up with us subsequently.

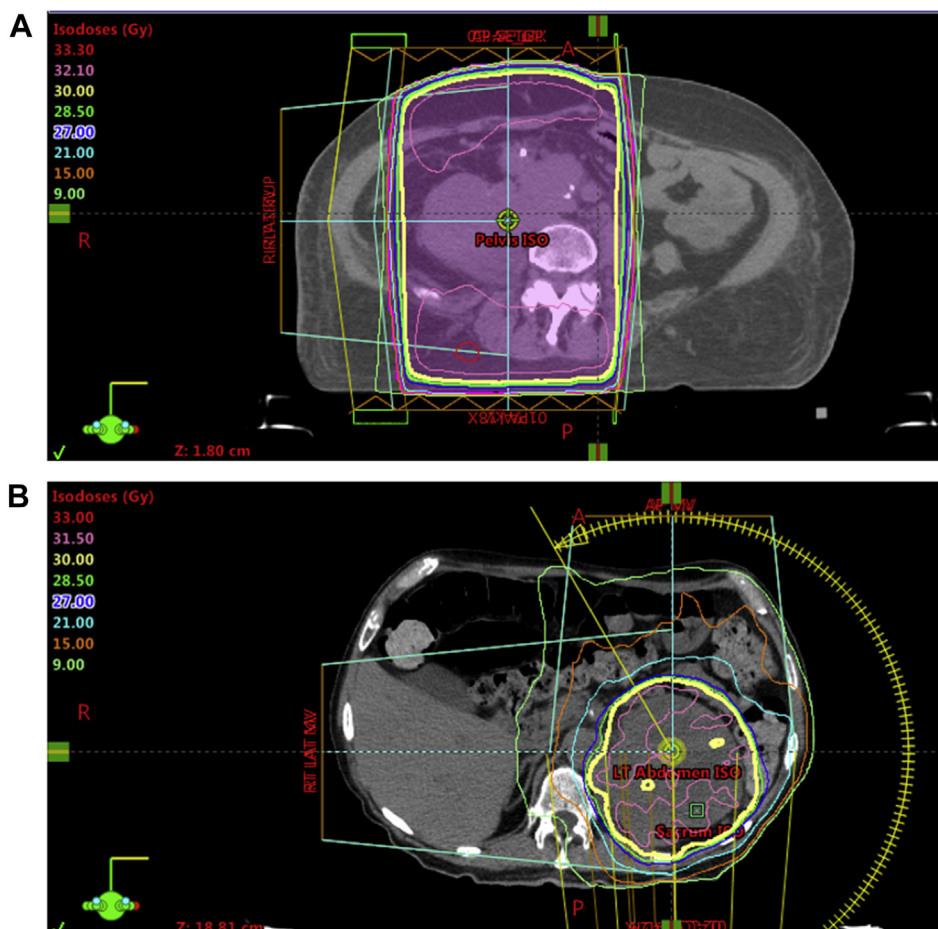


Figure 2 Dosimetry of the treated lesions. (A) Right psoas lesions treated by the anteroposterior/posteroanterior (AP/PA) technique to 30 Gy in 10 fractions. (B) Left adrenal lesion treated by the AP/PA technique to 30 Gy in 10 fractions.

Table 2 Selected preclinical studies of combination immunotherapy or combination immunotherapy and RT

Study	Therapeutic modality (s)	Tumor model	Results
Bartkowiak and Curran ¹²	α CTLA-4 and α 4-1BB	B16 melanoma	Increased survival; increased CD8 T-cell tumor infiltration and function; increased T-cell function; decreased Treg infiltration
Chen et al ¹³	α PD-1 and α 4-1BB	B16-F10 melanoma	Complete regression
Duraiswamy et al ¹⁴	α PD-L1 and α 4-1BB	ID-8 adenocarcinoma	Increased survival; increased T-cell tumor infiltrate and function; decreased Treg infiltration
Belcaid et al ⁹	RT and α 4-1BB	EMT6 mammary carcinoma M109 lung carcinoma	Decreased tumor burden
Shi and Siemann ¹¹	Focal RT/ α 4-1BB/ α CTLA-4	GL261 glioma	Increased long-term survival; increased T cells in brain; established protective immunity
Kroon et al ¹⁵	RT/ α PD-1/ α 4-1BB	BRAFV600-M melanoma	Increased efficacy when compared with IL-2 or α CTLA-4/ α PD-1 therapy
Benaduce et al ¹⁰	RT and 4-1BB aptamer	4T1 mammary carcinoma	Equivalent tumor controlled compared with 4-1BB mAbs; decreased liver and spleen CD8 T-cell infiltrates

IL, interleukin; mAbs, monoclonal antibodies; RT, radiation therapy; Treg, regulatory T cell.

Discussion

This is, to our knowledge, the first case report to demonstrate an unusual postradiation response with RT and 4-1BB agonist. This suggests a potential benefit of combining immunomodulation of 4-1BB with RT treatments in the future. The capacity of RT to augment dormant tumor immune responses via the 4-1BB pathway was initially demonstrated by Shi and Siemann,¹¹ who determined that high doses of radiation can induce expression of 4-1BBL on murine tumors. This seminal research demonstrated that single dose or multiple, fractionated doses of radiation given before systemic administration of 4-1BB agonist induces partial tumor regression.¹¹ Other preclinical studies have also established the efficacy of targeting this pathway as an effective technique to elicit a strong antitumor immune response (Table 2). Despite early success, triggering of high-grade liver inflammation by 4-1BB agonists has slowed its clinical development.¹² Although liver toxicity is a major concern, coupling lower doses of 4-1BB agonists and RT with other therapeutic modalities could potentiate a stronger antitumor responses while reducing the severity of 4-1BB-associated toxicity.

Recent preclinical publications have reported that incorporating RT into multimodality immunotherapy approaches can increase efficacy of treatment. The application of RT and 4-1BB agonist in conjunction with CTLA-4 blockade yielded superior long-term survival and protective antigen-specific memory response in a murine glioma model compared with RT alone or combination of 4-1BB and CTLA-4.⁹ Kroon et al recently

demonstrated that concomitant targeting of PD-1 and 4-1BB improves the effectiveness of RT in a mouse model of human melanoma.¹⁵ Interestingly, this study demonstrated that the combination of RT and blockade of PD-1 and stimulation of 4-1BB may be superior compared with currently tested combinations of RT with either α -CTLA-4 or α -PD-1 mAbs. Grouping RT with multiple immune-modulating therapies not only shows cooperative and synergistic therapeutic benefit, but may also allow for decreasing doses of RT and/or immunotherapy agents, potentially leading to reduced adverse reactions.

An alternative way of targeting the 4-1BB pathway entails using oligonucleotide aptamer technology. Aptamers are single-stranded oligonucleotides that are capable of binding a given target protein.¹⁶ Combination of RT with 4-1BB aptamer exhibited equivalent tumor control compared with RT with 4-1BB mAb in a murine tumor model. Moreover, 4-1BB aptamer treatment lacked the significant pathology associated with systemic administration of 4-1BB mAbs, suggesting a superior therapeutic index.¹⁰ Although still early, 4-1BB aptamer therapy may provide an alternative to costimulatory mAbs to cooperate with existing RT-checkpoint blockade therapy, with the added benefit of limiting potential toxicity.

With regard to this case, a possible confounding factor is the multiple previous interventions using immunotherapies before administration of 4-1BB mAb and RT. It is impossible to elucidate how these previous therapies affected the patient's response to 4-1BB/RT; however, as suggested by preclinical murine studies, the combination of multiple modalities used in this patient may have had a synergistic

effect that resulted in the exceptional response reported here. At the very least, it appears that the combination of 4-1BB mAb and RT yielded a significant reduction in tumor size in the patient presented in this report.

The impressive antitumor potential of 4-1BB is now being tested in multiple clinical trials. Phase I clinical trials that include monotherapy with 4-1BB mAbs (BMS-663513) or combination therapy, including use of 4-1BB mAbs with α -PD-1 mAbs (NCT02253992), are underway with results pending; however, to date, no trial has been designed to examine the efficacy of combining RT with 4-1BB blockade. Based on pre-clinical data from murine tumor models and the results presented here, radiation combined with 4-1BB agonists may have a unique and potent effect, in addition to other therapies combined with 4-1BB. Further research is warranted before this can be clinically implemented.

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