

Thinking Outside the Field: Two Cases of RT+ICI Synergy in Melanoma

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Case Report

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Abstract

While combination radiotherapy (RT) and immunotherapy is not novel there is still much to learn about this approach. Some initial pre-clinical and clinical evidence suggests triple therapy with RT and dual immune checkpoint blockade (anti-CTLA-4 + anti-PD-1/PD-L1) is a complimentary technique. We present two cases using the same novel regime of combination RT plus nivolumab and ipilimumab to treat metastatic melanoma. In both cases the burden of disease was significant within a lower extremity. Additionally, in both cases using this treatment plan, we were able establish sustained local disease control with additional systemic benefit which allowed both patients to avoid significant debility from surgical amputation. Given the response and safety we observed, this technique could be used as a potentially safe approach for future patients who are not eligible for traditional RT palliation or clinical trials.

Case 1 Summary

Mr. E was diagnosed with Stage IIIA (T3aN2aM0, AJCC 7th edition) BRAF wildtype melanoma in the right thigh at age 66 in June 2013. He was otherwise healthy. Wide local excision (WLE) and sentinel lymph node (SLN) biopsy was performed followed by right inguinal lymph dissection, showing negative margins and micrometastases in 3 of 26 lymph nodes. Positron emission tomography (PET) scan revealed no distant metastasis at that time.

In September 2014, right pelvic/external iliac and obturator lymphadenectomy was performed due to asymptomatic regional recurrence in his right inguinal nodal basin that was detected on surveillance PET scan. Five of 14 inguinal and external iliac and 1 of 4 right obturator lymph nodes were positive for metastasis with extranodal extension, and adjuvant radiation to the right external iliac nodal area (48 Gy in 20 fractions) was delivered without further systemic therapy.

In January 2015, ipilimumab (IPI) was initiated after asymptomatic recurrence near the right iliacus muscle was detected on PET scan. After 4 cycles of IPI, treatment was transitioned to pembrolizumab (PEM) due to disease progression. Concurrent palliative radiation 40 Gy in 10 fractions to the pelvis and 30 Gy in 10 fractions to T2 spinal metastasis was delivered. Near complete response was seen after 4 cycles of PEM (Fig. 1A).

Maintenance PEM was given until June 2016, when Mr. E developed innumerable soft tissue metastases throughout the right lower extremity (RLE) as well as new lesions in the chest wall, right lung, and left adrenal gland (Fig. 1B). Combination of paclitaxel/PEM was started.

Unfortunately, Mr. E developed rapid disease progression in the RLE after 2 cycles of chemo-immunotherapy (CIT) (Fig. 1C) with marked pain and rapid swelling from his large disease burden. He experienced a severe tightness, tingling and burning sensation in the RLE with weakness and decreased mobility. Potential palliative amputation was a possibility if rapid disease control was not obtained. After multi-disciplinary discussion, concurrent immunotherapy with dual immune checkpoint inhibitors

(Nivolumab (NIVO) 1mg/kg and IPI 3mg/kg every 21 days) and radiotherapy (RT) was pursued despite technical difficulties for disease palliation and avoidance of debilitating surgery.

Using Volumetric Modulated Arc Therapy (VMAT), a total of 40 Gy was delivered in 10 fractions in a two split-course of 20Gy, concurrent with 2 NIVO/IPI infusions 21 days apart. VMAT was used to treat the rind of soft tissue involved with melanoma while sparing the core of the extremity to reduce the risk of lymphedema and bone marrow suppression. The RT treatment plan required 3 matching plans (upper, mid, lower leg) with 3–4 partial arcs per plan (Eclipse treatment planning system, Varian Medical Systems; Fig. 1D). Patient specific quality assurance was performed using an ion chamber array which confirmed that the dose delivered agreed with the plan. Radiotherapy treatment was subsequently delivered using a TrueBeam linear accelerator (Varian Medical Systems) with image guidance. NIVO/IPI therapy was continued beyond RT per standard of care (SOC).

Mr. E tolerated the concurrent NIVO/IPI + RT well without any new onset adverse events including immune-related adverse events (irAEs) or cytopenia. He enjoyed marked clinical improvement in the RLE as well as remarkable objective response on PET scan obtained 10 weeks after RT in November 2016 (Fig. 1E) which was sustained 6 weeks later (Fig. 1F). With the exception of worsening of his new brain metastases, Mr. E experienced a few months of stable systemic control until March 2017 when he developed multiple soft tissue lesions in the chest wall, axillae and abdomen with bilateral adrenal metastasis. Interestingly, his right lower extremity continued to exhibit excellent local disease control. He underwent focal RT to the bilateral adrenal metastases and focal stereotactic radio surgery to the brain metastasis then subsequent whole-brain radiation and transitioned to Temozolomide therapy. Ultimately, he succumbed to his CNS melanoma burden in May 2017.

Case 2 Summary

Mr. B had a past medical history that was significant for aplastic anemia treated with bone marrow transplant and total body irradiation (TBI) at the age of 12. He later developed TBI-induced skin change, graft-versus-host disease of the skin that resulted in skin sclerosis, as well as multiple non-melanoma skin cancers. In 2014 at the age of 41, he developed a T2a desmoplastic melanoma in the posterior left calf with no distant metastasis, for which he had WLE and routine follow up with surveillance PET scans. In early 2017, Mr. B developed multiple skin lesions in the left calf and left thigh and was referred to our clinic in March 2017 for further management. PET scan at that time showed multiple skin and subcutaneous soft tissue metastases throughout the left leg (biopsy confirmed, BRAF wildtype), as well as bilateral inguinal and scrotal metastases (Fig. 1G). Systemic treatment with PEM was initiated. After 4 cycles of PEM, disease progression was seen throughout the left lower extremity (LLE), left inguinal and hip gluteal region (Fig. 1H). Therefore, carboplatin/paclitaxel was added to PEM in July 2017. Despite initial mixed response, in November 2017 significant disease progression was seen after 6 cycles of CIT combination, including extensive diffuse disease involvement in the LLE with involvement of the bilateral inguinal areas, iliac chain lymph nodes and perineum (Fig. 1I). Mr. B experienced severe swelling and pain in the LLE, with drainage and odor from multiple large raised soft tissue lesions, which significantly

limited his mobility and quality of life (QOL). After multi-disciplinary discussion, concurrent RT with NIVO 1mg/kg and IPI 3mg/kg every 21 days was initiated in December 2017 for symptom palliation and QOL improvement. Similar to case 1, a total of 40Gy was given in 10 fractions (split course of 5 fractions) using VMAT, delivered concurrently with 2 dual-ICI infusions 21 days apart. Mr. B tolerated the concurrent NIVO/IPI + RT well without dose-limiting adverse events including cytopenia or irAE. ICI therapy was continued beyond RT completion per SOC. Patient experienced symptomatic relief shortly after RT. PET scan performed in March 2018 showed dramatic disease response in the LLE (Fig. 1K). Unfortunately, disease progression beyond the RT field, including pelvic abdominal and thoracic areas, was seen. Mr. B received further CIT, with continued disease improvement in the LLE and mixed response in other areas (Fig. 1L). Ultimately, he deceased in August 2018.

Discussion

Studies have shown RT efficacy in the treatment of melanoma dating back to the 1970s.^{1,2} Typically, it is used in the context of adjuvant therapy following resection in early stage disease or as palliation in late stage i.e., spinal cord compression, brain metastasis, or metastasis causing pain, bleeding, or obstruction. RT local clinical benefit relies on induced DNA damage causing apoptosis.³ Abscopal effect refers to a rare phenomenon of tumor regression at a site distant from the primary site of RT and has been shown in multiple cancers including melanoma.⁴⁻⁷ There is renewed interest in the immunomodulatory effects of RT in the era of immunotherapy because pre-clinical models suggest that RT can improve efficacy of immune checkpoint blockade and conversely ICI can increase the efficacy of RT not only locally but systemically.⁸⁻¹⁰ Research shows that triple therapy (RT + anti-CTLA-4 + anti-PD-1/PD-L1) such as what was used in our patients is not redundant and is instead complimentary. Clinical models suggest that RT increases diverse T cell activation through increased local expression of MHC class 1 molecules which improves the antigen presenting ability of APCs.¹¹⁻¹³ Then CTLA-4 blockade initiates the suppression of Treg cells, thus increasing the ratio of CD8/ Treg and the addition of PD-1/PD-L1 inhibition increases the proportion of overall CD8 + T cells.¹⁴ These activated CD8 + T cells can migrate through the body and infiltrate the metastases outside of the irradiated field when a certain threshold amount is reached causing systemic anti-tumor benefit.¹⁴

Still, very little is understood clinically about combination RT + anti-CTLA-4 + anti-PD-1/PD-L1. A 24 patient pilot study of RT in combination with NIVO/IPI in locally advanced head and neck squamous cell carcinoma showed feasibility of RT with ICI and resulted in no loco-regional relapses in 20 high-risk patients. No patients in the study developed grade 4/5 adverse events during combination therapy.¹⁵ Similarly, a prospective study of Durvalumab (anti-PD-L1) and Tremelimumab (Anti-CTLA-4) in combination with RT and a separate Phase 2 study of NIVO/IPI + RT in metastatic colorectal cancer showed durable activity with patients experiencing benefit outside the local radiation field and similar toxicities to those on dual ICI therapy alone.^{16,17}

In melanoma specifically, a recent Phase I study of NIVO/IPI + RT in advanced melanoma patients was pursued to address the safety of this combination.¹⁰ Two dosing schedules were used. Both used standard NIVO 1mg/kg and IPI 3mg/kg every 21 days, while Cohort A received extracranial RT with a dose of 30 Gy in 10 fractions and Cohort B received 27 Gy in 3 fractions. Patients responded to treatment outside of the irradiated volume (Cohort A 5/10; Cohort B 1/9). No patients had progression of irradiated metastases. Safety profile showed no marked difference between SOC NIVO/IPI and NIVO/IPI + RT and RT did not compromise the ability of patients to receive intended combination immunotherapy.¹⁰ Sample size was too small to address questions of improved efficacy.

Because there have been few studies in this arena, the best treatment regimen including optimum dose and schedule is not known. We do know that the effects of RT are dose dependent, and the manner in which the total RT dose is fractionated may be of immunologic clinical relevance.¹⁸ More direct comparison studies of various RT regimens and outcomes would be beneficial. Our patients received the same novel dosing schedule for NIVO/IPI + RT which included a total of 40Gy in 10 fractions given by a split course of 5 fractions each delivered concurrently with 2 dual-ICI infusions 21 days apart. Given the relative radioresistance of melanoma, a high total RT dose with a dose per fraction size of 8–9 Gy is typically used for melanoma metastases.¹⁰ The dramatic and fairly rapid response we saw in these two cases with extensive disease burden treatment is likely to be the result of immunomodulation caused by the combination therapy rather than RT alone. Also, consistent with other reports, RT/ICI provided excellent/prolonged disease control within the RT field for our 2 cases.

There are currently no reliable biomarkers to help identify patients that may benefit from this combination therapy or to help trend clinical benefit with therapy. Current small sample sizes do not allow proper statistical analysis for associations between immune correlates and clinical outcomes and instead are preliminary and descriptive. In the advanced melanoma Phase 1 NIVO/IPI + RT study they noted that responders generally seemed to have increases in TCR diversity and saw increases in the proportion of Ki67 + PD1 + CD8 T cells and Ki67 + CD4 + T cells with the combination treatment.¹⁰

One known subset of therapy-responsive effector CD8 + T cells express the chemokine receptor CX3CR1. These T cells have the ability to withstand chemotherapy toxicity and are increased in patients with metastatic melanoma who respond to combination chemoimmunotherapy.^{19,20} Clinical models suggest that these CX3CR1 + CD8 + T cells are PD-1 therapy–responsive effector CD8 + T cells capable of entering tumor tissues and exhibiting anti-tumor effects.¹⁹ We also know CX3CR1 + CD8 + T cells increase after effective combined CIT and we wondered if we would see changes in the setting of NIVO/IPI + RT. We collected CX3CR1 + CD8 + T cell measurements for Mr. E prior to, during and after radiation (Fig. 2). Consistent with the low CX3CR1 + T cells seen in patients who failed to respond to CIT in our previous study, CX3CR1 + CD8 + T cell level was low prior to RT when Mr. E experienced significant disease progression with CIT. This T cell subset increased concurrent to RT + ICI when he clearly experienced significant anti-tumor benefit. The subsequent decrease of CX3CR1 + CD8 + T cell seen after NIVO/IPI + RT completion is likely due to the tissue migration of this effector T cell subset. Although additional

studies in future prospective trials is needed, our results suggest that CX3CR1 + CD8 + T cell measurement, which can be obtained with simple peripheral blood draw, could be used as a potential biomarker for response monitoring in these patients and guide the design of rational ICI/RT combination strategy.

Although radiotherapy and immune checkpoint inhibition is not a novel approach, we are continuing to learn more about how triple therapy (RT + anti-CTLA-4 + anti-PD-1/PD-L1) affects both the tumor microenvironment and the systemic tumor burden. Recall that both patients failed multiple lines of systemic therapy, including CIT, and responded to subsequent RT + ICI. For these heavily pre-treated patients with extensive disease burden that is not suitable for a traditional RT regimen, we were able to alleviate significant side effects and avoid the debility of surgery using our triple combination regimen with novel RT planning. Our patients did very well with their regimen. Neither patient developed grade 3 or above toxicities from the combination strategy including Mr. B who was fairly high risk for complications given his other comorbidities. Neither patient developed significant cytopenias given the lack of radiated bone marrow areas.

Although our treatment strategy needs to be validated in a prospective study, given the response and safety we observed here, this can be used as a potentially safe approach, especially in cases that a typical RT approach is not feasible and patients are not eligible for trials.

Methods

The following panel of antibodies was used for analysis of PBMC populations: CD8-PE-Cy7 (BD Pharmingen, clone RPA-T8, catalog 304006), CD11a-APC (BioLegend, clone HI111, catalog 301212), CX3CR1-APC/Cy7 (BioLegend, clone 2A9-1, catalog 341616), Granzyme B-PerCP (Novus Biologicals, Danvers, Massachusetts, clone CLB-GB11, catalog NBP1-50071PCP). CD8 + T-cells were first stained for surface markers followed by intracellular staining. Flow cytometry data were collected on a CytoFLEX LX (Beckman Coulter, Atlanta, Georgia). Flow cytometry analysis was performed with FlowJo software 10.4 (Tree Star, Palo Alto, California).

Declarations

COI: The authors report no conflicts of interest.

Author Contribution: T.D. analyzed the results and wrote the manuscript. H.Z. and H.D. performed the biospecimen analysis and edited the manuscript. M.G. and S.P. provided directed patient care and wrote the manuscript. Y.Y. provided direct patient care, designed the study, analyzed the results and wrote the manuscript.

Data Availability: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with Ethical Standards: Participants provided written informed consent to take part in the study. Biospecimen collection was performed under the research protocol approved by the Mayo Clinic IRB Committee (15-000934) in accordance with regional and national guidelines.

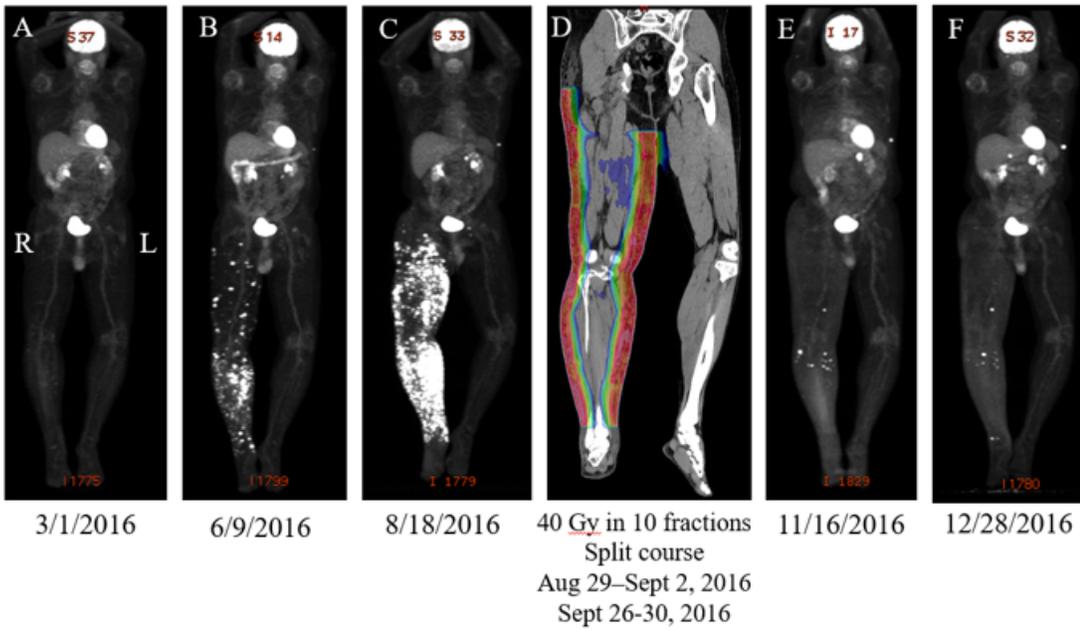
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Figures

Case 1: Mr. E PET/CT staging scans and RT planning (Fig 1A-1F)



Case 2: Mr. B PET/CT staging scans and RT planning (Fig 1G-1L)

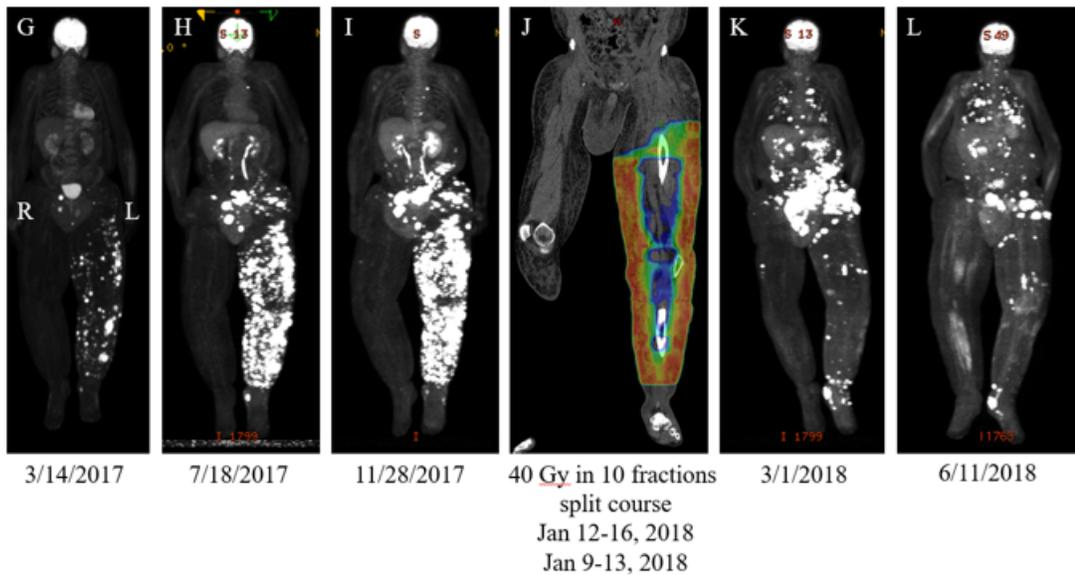


Figure 1

After 4 cycles of IPI, treatment was transitioned to pembrolizumab (PEM) due to disease progression . Concurrent palliative radiation 40 Gy in 10 fractions to the pelvis and 30 Gy in 10 fractions to T2 spinal metastasis was delivered. Near complete response was seen after 4 cycles of PEM

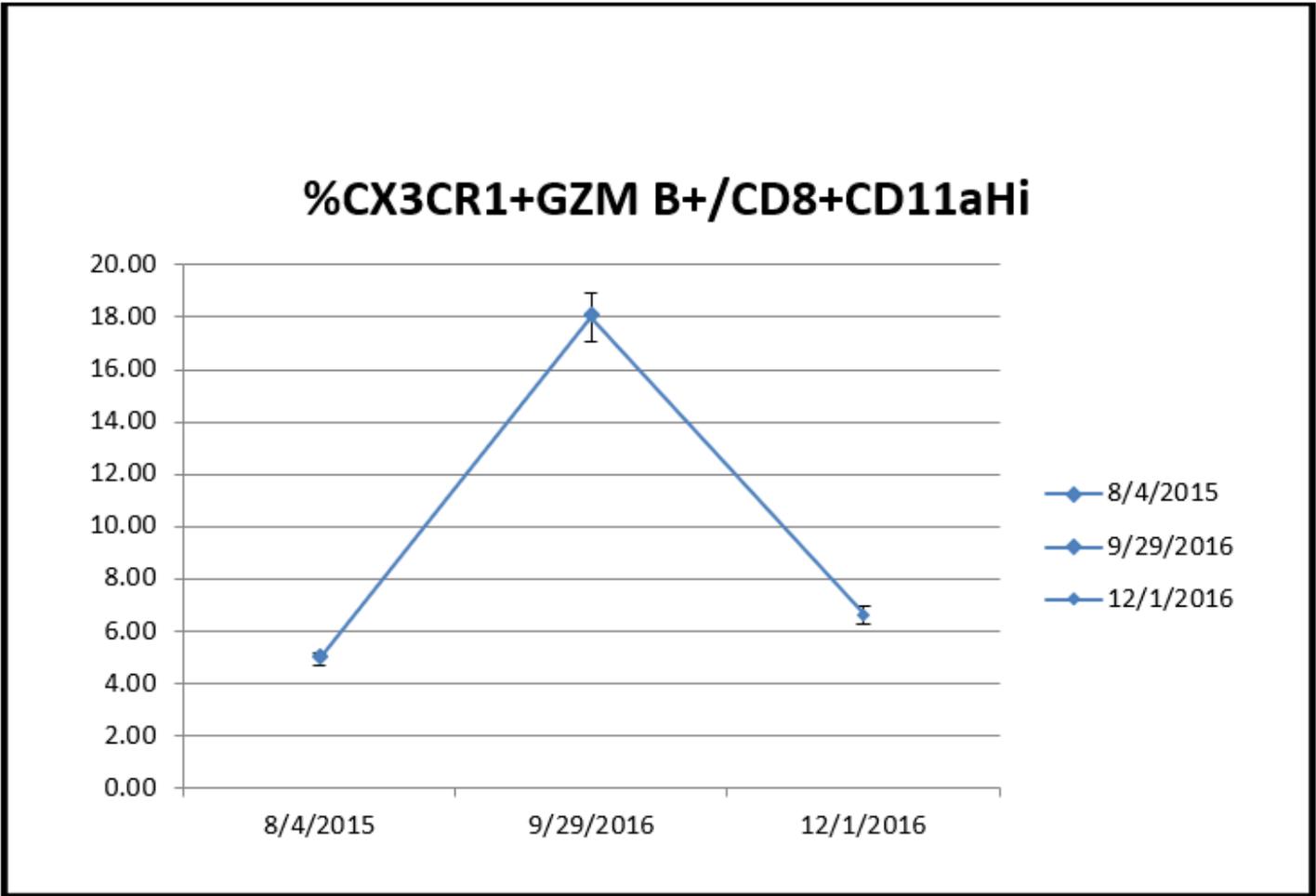


Figure 2

Therapy-responsive effector T-cell level prior to, during and after RT-ICI