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Combined modality neoadjuvant treatment for stage III/IV melanoma with PD-1 blockade plus radiation: A case series

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ABSTRACT

Purpose: Over the last 6 years, 8 treatments were FDA-approved for patients with distant metastatic cutaneous melanoma on the basis of prolonged overall survival. Several of these treatments are either FDA-approved or in advanced stages of clinical development in the adjuvant setting for patients with high risk for relapse melanoma. The neoadjuvant setting provides even greater opportunities to incorporate these treatments into a more effective multimodality management. While most neoadjuvant strategies involve single modality approach to date, the ability of radiation therapy to synergize with immunotherapies in distant metastatic melanoma should also be considered in the neoadjuvant setting.

Methods and results: 4 patients with unresectable stage III melanoma were treated with PD-1 inhibitors and concurrently received hypofractionated radiation therapy. This regimen not only rendered their surgery feasible, but also resulted in complete pathologic response in two of these patients without inducing any serious adverse events or surgical complications. Furthermore, we present clinicopathologic and molecular data that may in part explain differences in complete pathologic response among these four subjects.

Conclusions: In this limited case series, our neoadjuvant combined modality regimen was effective and well tolerated. Concurrent PD-1 blockade with radiation therapy that could readily be applied into daily oncology practice is not limited in particular patient subgroups (e.g. BRAFV600-mutant) and may have a better toxicity profile than concurrent immune checkpoint blockade.

1. Introduction

Over the past 40 years, neoadjuvant treatments have been explored across several solid organ malignancies to enhance tumor resectability and improve local control [1]. In cutaneous melanoma, neoadjuvant therapies for locoregional unresectable disease were only systematically investigated over the past 15 years, in part due to lack of effective systemic therapies for melanoma. In neoadjuvant trials employing immunotherapy regimens, clinical benefit was noted along with evidence of host immune response in tumor tissue and peripheral blood. However, the incidence of complete pathologic response, the gold standard surrogate of long-term clinical benefit, was low (< 15%) [2,3]. More recently, several case reports have shown promising clinical benefit of neoadjuvant MAPK inhibitors in patients with unresectable $BRAF^{V600}$-mutant melanoma [4].

Radiation therapy (RT) enhances cancer cell immunogenicity by upregulating MHC class I as well as pro-inflammatory and other pro-apoptotic effectors, among other mechanisms [reviewed in [5]]. A number of preclinical studies, case reports, and retrospective analyses have shown that there is an additional benefit if RT and immune checkpoint inhibitors (ICIs) are combined. In line with this synergy in distant metastatic melanoma we became interested to explore the clinical benefit of concurrent PD-1 blockade in combination with hypofractionated radiation therapy in patients with unresectable stage III/IV cutaneous melanoma. In this small case series we present clinical vignettes on 4 such patients who were treated with a PD-1 inhibitor in combination with radiation therapy. Demographic, pathologic and molecular information as well as details about the treatment schedule, outcome, and toxicities graded by the National Cancer Institute Common Terminology Criteria for Adverse Event version

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Table 1
Summary of patient characteristics.

Patient	Age, sex	AJCC staging	Molecular testing results[1]	TIL[2]	PD-1i used	RT used	Pathologic Response[3]	AE attributed to 1i[4]	AE attributed to PD-RT[4]	AE attributed to Surgery	Follow-up (months)
A	78, male	TxN3M0IIIC	$NRAS^{Q61H}$	Absent	Nivo, 2 mg/kg, 11 infusions	3,000 cGy in 5 fractions	CR	None	Dermatitis (G1)	None	6
B	58, male	TxN2bM0IIIB	$BRAF^{V600E}$ $TP53^{E286K}$ $PTEN^{K267*}$	Present non-brisk	Pembro 2 mg/kg, 7 infusions	3,000 cGy in 6 fractions	Non-CR	Fatigue (G1) Rash (G2) Thyroiditis (G2)	Dermatitis (G1)	Seroma	6
C	41, male	T4bN3M0IIIC	$NRAS^{Q61K}$	Present non-brisk	Pembro, 2 mg/kg, 12 infusions	5,500 cGy in 22 fractions	CR	Type I Diabetes Mellitus Hyperglycemia (G3)	Dermatitis (G2)	Dehiscence	16
D	54, female	TxN0M1a	$NRAS^{Q61K}$	Absent	Pembro 2 mg/kg, 5 infusions	3,000 cGy in 5 fractions	Non-CR	None	Dermatitis (G1) Cellulitis (G2)	Debridement of necrotic keystone advancement flap	5

Abbreviations: AJCC, American Joint Committee on Cancer; TIL, tumor-infiltrating lymphocytes; nivo, nivolumab; pembro, pembrolizumab; PD-1i, PD-1 inhibitory antibody; RT, radiation therapy; AE, adverse events; G, grading of toxicities according to CTCAE v4.03. **1**, Molecular analysis of the biopsied tumor was performed using the TruSight Tumor 26®-gene panel (Illumina). **2**, TIL density was semiquantitatively assessed (LGD, JBK) in representative hematoxylin and eosin-stained (H & E) tissue sections from corresponding tumors as absent, present non-brisk, and present brisk. No necrotic areas were found in the excised specimen in all four subjects. **3**, Complete pathologic response (CR) is defined as absence of viable tumor in any of the tissue blocks that were submitted for pathologic analysis. **4**. Treatment toxicity was graded according to the CTCAE v4.03).

4.03 (NCI-CTCAE v4.03) are presented in Table 1.

2. Case reports

2.1. Patient A

A 78 year-old white Caucasian male with no previous history of cutaneous melanoma presented with a painful right axillary mass that was associated with tingling and decreased range of motion. His physical exam was remarkable for sun-damaged skin as well as a 13 cm axillary mass and no suspicious pigmented skin lesions. Biopsy of the axillary mass confirmed metastatic melanoma; no tumor-infiltrating lymphocytes were seen. Molecular analysis of the biopsied tumor using the TruSight Tumor 26®-gene panel (Illumina) was significant for the presence of the $NRAS^{Q61H}$ mutation. Computed axial tomography (CT) of the chest, abdomen and pelvis with IV contrast was significant for a 10× 6×11 cm conglomerate of necrotic right axillary lymph nodes impinging on the axillary vessels (AJCC stage IIIC, TxN3M0). Given that his axillary disease was surgically unresectable, the patient was treated with nivolumab, 2 mg/kg IV every 2 weeks. Hypofractionated external beam RT (3,000 cGy divided in 5 fractions, administered every 2 days) [6] was initiated between the first and second ipilimumab infusion. He tolerated radiation therapy very will with only development of grade 1 dermatitis that was controlled with topical emollients. Preoperatively, the patient received a total of 11 infusions of nivolumab without development of any immune-mediated side effects. Following 6 nivolumab infusions and 8 weeks after the end of radiation, repeat CT scan with IV contrast showed that the right axillary mass had significantly decreased in size (4×3 cm) along with improvement in reported symptoms. Given that the axillary mass only minimally shrunk following 4 more nivolumab infusions (3×2 cm; Fig. 1), patient then subsequently underwentradical, level I–III, right axillary lymph node dissection, including portions of the pectoralis major muscle. Pathologic examination of the surgical specimens identified no viable melanoma cells. His surgical drain was removed six weeks after the surgery, and he had no post-operative complications. The patient elected to receive 9 more nivolumab infusions with no evidence of disease progression 6 months following axillary lymph node dissection.

2.2. Patient B

A 58 year-old white Caucasian male with no previous history of cutaneous melanoma presented with a history of a slowly enlarging, painful right axillary mass and an unintentional 15-pound weight loss. On physical examination, a 12 cm, fixed right axillary mass was noted and no suspicious pigmented skin lesions. Whole body CT scan with IV contrast was only significant for an 11×11×6 cm right axillary soft tissue mass along with a 1.7×1.5 cm lymph node adjacent to the

Fig. 1. Representative image from CT scan with IV contrast following 10 infusions of nivolumab and concurrent hypofractionated RT. Yellow circle shows the residual R axillary mass.