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Complete Local and Abscopal Responses from a Combination of Radiation and Nivolumab in Refractory Hodgkin's Lymphoma

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Abstract

Until recently, patients with relapsed Hodgkin's lymphoma after brentuximab vedotin (Bv) treatments had poor treatment outcomes. Checkpoint inhibitors such as nivolumab and pembrolizumab that bind to and inhibit programmed cell death protein-1 (PD-1), have demonstrated an overall response rate of 70% in Hodgkin's lymphoma patients; however, complete response is still low at 20% with median progression-free survival of 14 months. There are ongoing clinical studies to seek out synergistic combinations, with the goal of improving the complete response rates for the cure of Hodgkin's lymphoma. Although radiotherapy has a limited survival benefit in such refractory patients, several preclinical models and anecdotal clinical evidence have suggested that combining local tumor irradiation with checkpoint inhibitors can produce systemic regression of distant tumors, an abscopal effect. Most of these reported studies on the response with local conformal radiotherapy and checkpoint inhibitors in combination with the anti-cytotoxic T-lymphocyte associated antigen-4 (CTLA-4) antibody-ipilimumab are in melanoma. Here we report in our case series that the checkpoint inhibitors that block CTLA4 and B7-homolog 1 (B7-H1) or PD-1 in preclinical radiotherapy models have shown an increased the rate of tumor regression. Our case series demonstrates that combining local irradiation with anti-

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PD-1 checkpoint blockade treatment is feasible and synergistic in refractory Hodgkin's lymphoma. Correlative studies also suggest that the expression of programmed death-ligand 1 (PD-L1), DNA damage response and mutational tumor burden can be used as potential biomarkers for treatment response.

INTRODUCTION

One of the common mechanisms of immune escape by tumors is the downregulation or loss of the antigen-presenting major histocompatibility class I (MHC-I) molecules and the expression of checkpoint programmed cell death ligand 1 (PD-L1), a ligand for the immune checkpoint receptor programmed cell death protein-1 (PD-1) expressed by T cells. Several studies have demonstrated effective blocking of either PD-1 or PD-L1 with monoclonal antibodies, which led to their approval for clinical usage (1). Expression of PD-L1 (2) due to alteration in chromosome 9p24.1 is nearly universal in Hodgkin's lymphoma. This may underlie the high response rates observed with the checkpoint inhibitors, CheckMate 039 (3) and KEYNOTE 013 (4) in relapsed/refractory (R/R) Hodgkin's lymphoma. However, the complete response (CR) is approximately 20% and there is a need to achieve a stronger and more predictable response with the goal of increasing cure rates in R/R Hodgkin's lymphoma. In addition to PD-L expression levels (1, 3, 4), T-cell infiltration into the microenvironment, tumor mutational load [a rich source of neoantigen repertoire (5)] and cytokine activation have been shown to play a major role in predicting which patients will respond to currently effective checkpoint inhibitors against PD-1/PD-L1. From the time when the abscopal effect was first described by Mole (6), there has been increasing evidence of the immunotherapeutic potential of ionizing radiation due to its ability to induce tumor antigen release during cancer cell death and promote pro-inflammatory signals that trigger tumor-specific T cells (7–10). Anecdotal examples of the abscopal effect, systemic regression of tumors or metastasis outside the local radiation field have been reported (3, 9–12). Whereas salvage radiotherapy can induce durable local control in only a subset of R/R Hodgkin's lymphoma (13), the accelerated progress in tumor immunotherapy has prompted clinical studies that combine radiation with checkpoint inhibitors so as to predictably reproduce this phenomenon. Our case series reported here illustrates the potential of these two modalities, combined, to produce a long-lasting CR in patients with relapsed/refractory nodular sclerosing Hodgkin's lymphoma (R/R NSHL) who otherwise have an extremely poor prognosis.

MATERIALS AND METHODS

The data presented here were obtained from three patients with chemoresistant and brentuximab vedotin (Bv) refractory CD30-positive NSHL treated with radiation and nivolumab in three different sequences: 1. radiotherapy followed two months later by nivolumab; 2. radiotherapy followed by nivolumab; and 3. nivolumab for one treatment followed by concomitant radiotherapy and nivolumab. We also performed correlative studies such as immunohistochemistry for PD-L1, tumor mutation testing at Foundation Medicine (Cambridge, MA) and experiments for DNA repair.

Chromosome studies were performed in phytohemagglutinin-stimulated peripheral blood cells. Heparinized peripheral venous whole blood from individuals were incubated at 37°C, in RPMI medium supplemented with 10% fetal bovine serum and phytohemagglutinin. Metaphase chromosomes were prepared by standard procedures, as described elsewhere (14). Giemsa-stained chromosomes from metaphase spreads were analyzed for chromosome aberrations (15). Telomeres and centromeres in metaphase spreads were detected by fluorescent *in situ* hybridization (FISH) with a telomere- and centromere-specific probe, as described elsewhere (15, 16).

RESULTS

All three patients achieved durable complete local and abscopal responses. The histopathology in all the patients demonstrated high PD-L1 expression: patient no. 2 demonstrated a mutation in the *STAT6* gene, amplification of a “neoantigen” Erb-B2 receptor tyrosine kinase 2 (*ERBB2*) along with DNA damage response; and patient no. 3 showed a tumor mutation burden (TMB) score of 8.15. Although only two out of three patients received hematopoietic cell transplantation, all three patients with refractory disease have achieved a durable CR on restaging PET scans with median follow-up of two years (Figs. 1–4).

Patient no. 1 is a 21-year-old male with heavily treated, refractory stage IVB classic NSHL who failed with adriamycin, bleomycin, vinblastine and dacarbazine (ABVD) and with etoposide, methylprednisolone, cytarabine and cisplatin (ESHAP) and managed to achieve a partial remission with BCNU, etoposide, cytarabine and melphalan (BEAM) high-dose chemotherapy followed by peripheral blood stem cell transplant in June 2013. Later the patient received eight cycles of brentuximab with progression and more chemotherapy including three cycles of ifosfamide, gemcitabine, etoposide and vincristine (IGEV) and cyclophosphamide, vincristine, procarbazine and prednisone (COPP) chemotherapy. The patient received palliative 20 Gy radiotherapy for five days to L2 and left iliac crest lesions in February 2015. A PET scan in April 2015 still demonstrated multiple sites of adenopathy as well as osseous lesions (Fig. 1A). The patient received nivolumab and demonstrated a drastic reduction in alkaline phosphatase (Fig. 1B), as well as dramatic improvement as seen in the PET scan after just two treatments (Fig. 1B); and the patient demonstrated a complete response after four months of treatment with complete resolution of adenopathy and all lytic lesions (Fig. 1C). Treatment response was also indicated by normalization of hemoglobin levels (Fig. 5). After receiving nivolumab for six months, the patient underwent a matched sibling allogeneic stem cell transplantation in October 2015. The patient’s course was complicated by grade II pulmonary graft-vs.-host disease, which responded to appropriate treatment. The patient is relapse-free 37 months from the first nivolumab treatment.

Patient no. 2 is a 34-year-old Caucasian male with refractory stage III NSHL, diagnosed in December 2011, who received ABVD chemotherapy, achieving complete remission. He had a biopsy proven relapse a year later and received salvage chemotherapy with ifosfamide, carboplatin and etoposide (ICE) for three cycles, achieving a CR. The patient underwent stem cell mobilization in October 2013, followed by BEAM-conditioning regimen and received autologous stem cell transplantation in November 2013. A year later, the PET scan

in June 2015 showed further marked uptake in preaortic and pelvic lymph nodes. The patient was treated with four cycles of brentuximab vedotin, with increasing pelvic lymphadenopathy and standardized uptake value (SUV) on the PET scan (Fig. 2A). For this disease progression, the patient received 36 Gy in 20 fractions. The PET scan after radiotherapy showed improvement in the SUV with persistent lymph nodes (Fig. 2B), and patient was subsequently initiated on nivolumab for six cycles; the PET scan in September 2016 showed CR (Fig. 2C). The patient is relapse-free 27 months from his first nivolumab treatment.

Patient no. 3 is a 23-year-old college student diagnosed with refractory stage IIA NSHL from the biopsy of a $12 \times 5.6 \times 3.8$ cm mediastinal mass. The patient was initiated on ABVD with restaging PET scan after cycle 2 showing some shrinkage to $7.5 \times 5.0 \times 5.5$ cm. However, after cycle 4, the mass increased in size to $7.7 \times 5.2 \times 5.7$ cm and with a higher SUV. The patient subsequently received three cycles of brentuximab vedotin. Due to disease progression, the patient was subsequently given two cycles of ICE salvage therapy and had no response (Fig. 3A). The patient was then initiated on nivolumab in April 2016. After two courses, he received concurrent 40 Gy in 20 fractions to cervical and mediastinal lymph nodes. The patient completed 12 doses of nivolumab, and a PET scan in September 2016 showed no evidence of lymphoma (Fig. 3B). The patient underwent a BEAM-conditioning regimen, received his autologous stem cell transplantation without complications in October 2016 and remains in CR, 23 months from achieving CR.

Several tumor features, including the expression of PDL1, and mutational burden, have been reported as biomarkers (1, 3–5). Therefore, we tested for these features in our case series. All patients uniformly expressed PD-L1 by immunohistochemistry; only the sample from patient no. 2 expressed EBER (Epstein-Barr virus-encoded small RNA) by *in situ* hybridization. Next, we sought to understand the genetic alterations in the Cancer Genomic exome to establish mutational burden in the tumors. Tumor mutation burden (or mutation load) is a measure of the number of somatic protein coding base substitution and indel mutations occurring in a tumor specimen with readouts given as a TMB score. Two of the three patients underwent next-generation sequencing; patient no. 2 showed ERBB2 amplification and patient no. 3 showed a mutation in the *STAT6* gene at Q286R. Patient no. 2 had TMB that could not be determined as the detection was <30%, while patient no. 3 had an intermediate TMB with 8.15 mutations per megabase (Table 1). Finally, we analyzed peripheral blood mononuclear cells for radiation-induced residual DNA damage, as a surrogate marker for response (14). First, to determine whether chromosomes are intact, telomere FISH was performed, and centromere FISH was used as an internal control (Fig. 6A). As shown in Fig. 6A, only patient no. 2 showed frequent loss of telomeres as indicated by arrows, while patients no. 1 and 3 (not shown) were normal. We evaluated the mitotic index which were statistically lower in patient no. 2. (Fig. 6B). Cells treated with radiation were evaluated for metaphase aberrations using a standard protocol (17), which was found to be higher in patient no. 2 (Fig. 6C).

DISCUSSION

NSHL often exhibits chromosome 9p24.1 amplification correlating with overexpression of PD-1 ligands and immune evasion (2). All three patients received a combination of radiation to the bulky tumor and nivolumab and achieved a sustained CR as shown in the Swimmer's plot (Fig. 4) between 23 and 37 months. Based on these observations, we hypothesize that the addition of PD-1 inhibitor overcame the immunosuppressive barrier, enhanced the T-cell response and promoted both the local and abscopal effect observed in the patients.

Additional features in the tumor environment that likely augmented the immune response were 1. *STAT6* mutations in patient no. 2 and amplification of a "neoantigen" *ERBB2* in patient no. 3; 2. intermediate tumor mutational burden in patient no. 3; and 3. chromosomal aberration response in PBMCs that marks for the active T-cell population. Similar beneficial immunobiologic effects have been shown in clinical reports focused on melanoma (8–10). In their case report of the ipilimumab-treated patient, the authors detected NY-ESO-1 expression by immunohistochemistry, and could show an increase in seroreactivity to the protein before and after the treatment. More importantly, they demonstrated that even though the frequency of NY-ESO-1 specific interferon- γ producing CD4 cells increased with the ipilimumab treatment, the regression in the tumor occurred only after radiotherapy (9). In the other case report, Stamell and colleagues reported complete regression of brain metastases with concurrent stereotactic radiosurgery and ipilimumab for more than seven years (10). In addition, there was a demonstrable increase in antibodies against melanoma antigen A3.

One possibility to consider is that the single-agent activity of nivolumab and/or the radiation may have otherwise contributed to our patients' response. In the single-agent Hodgkin's lymphoma studies with PD-1 inhibitors, the CR rates were in the range of 17–22% in patients who progressed after brentuximab vedotin and autologous stem cell transplant (3, 4). In a single case report by Michot and colleagues (12) there is description of an abscopal effect in a patient with refractory Hodgkin's disease after progressing on pembrolizumab for almost a year. The patient received palliative localized radiation, with a total of 30 Gy to the progressive right hilar, mediastinal lymph node between the two infusions. The patient's symptoms resolved and a subsequent PET scan showed resolution beyond the hilar area. It is now apparent from these case reports that the combination of local radiation with anti-PD-1 antibodies indeed can lead to higher rates of response from the abscopal effects. The German Hodgkin's Study Group (GHSG) now plans to conduct a 100-patient, multicenter, phase 2 study in early-stage favorable classical Hodgkin's lymphoma with six cycles of anti-PD-1 antibody and 20 Gy involved site radiotherapy (18, 19).

The key points from this case series are: 1. combining local irradiation with anti-PD-1 checkpoint blockade provided a synergistic response in refractory Hodgkin's lymphoma; 2. correlative studies suggest the expression of PD-L1, DNA damage response and mutational tumor burden as potential biomarkers for response. Future translational studies are warranted to determine the dose fraction of radiation, the timing of immunotherapy, biomarkers (20) and the safety profile of such a combination.

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FIG. 1.

Patient no. 1. Positron emission tomography (PET) scan assessment of tumor burden before and after nivolumab administration. Panel A: Pretreatment PET scan reveals multiple sites of disease. Shown are: confluent right axillary adenopathy (top panel; SUV 14.2) and bilateral iliac lytic metastases (bottom panel; right iliac SUV 19.9; left iliac SUV 15.2). Panel B: Follow-up PET scan during treatment shows marked improvement (axillary SUV 3.0; right iliac SUV 3.0). Panel C: PET scan four months after treatment shows complete response.

FIG. 2.

Patient no. 2. Panel A: Pretreatment PET scan reveals multiple abnormal lymph nodes. Shown here are paraaortic (top panel; 4.1×2.6 cm, SUV 15.5) and left common iliac (bottom panel; 2.6×2.1 cm, SUV 14.8). Panel B: Three months postirradiation to lymph nodes, PET scan shows complete response, with small, ametabolic nodes: 1.3×1.0 cm paraaortic lymph node and 1.0×0.7 cm left common iliac node. Nivolumab was started. Panel C: Seven months later, PET and CT scans both show complete response.

FIG. 3.

Patient no. 3. Panel A: Pretreatment PET scan shows numerous abnormal lymph nodes in the neck and chest. Shown are: right supraclavicular/retroclavicular lymph node (top panel; 2.0 × 1.4 cm, SUV 7.7) and right upper paratracheal node (bottom panel; 3.6 × 2.4 cm, SUV 10.1). Panel B: PET scan six months later. After nivolumab treatment and neck and chest irradiation, scan shows complete response on PET, with small-to-absent residual nodes on CT. Largest lymph node is in right upper paratracheal (bottom panel; 1.0 × 1.0 cm).

FIG. 4.

Swimmer's plot showing duration of treatment and follow-up. Patient no. 1 received nivolumab after irradiation, received treatment for six months after achieving CR in four months, followed by matched sibling allogeneic peripheral stem cell transplant; follow-up duration is 31 months. Patient no. 2 received nivolumab after radiotherapy, achieved CR in two months and received treatment for 12 months after achieving CR in two months; follow-up duration is 17 months. Patient no. 3 received nivolumab for one cycle, followed by concurrent irradiation and nivolumab, received treatment for six months after achieving CR in four months, followed by high-dose chemotherapy peripheral stem cell rescue; follow-up duration is 18 months.

FIG. 5.

Treatment response in patient no. 1 with normalization of alkaline phosphatase and hemoglobin. NV = nivolumab.

FIG. 6.

Cytogenetic analysis. Panel A: Metaphase chromosomes from blood of patient no. 2 showing centromeres and telomeres. Arrows indicate telomere loss. Panels B and C: Mitotic index and chromosomal aberrations, respectively, from patient peripheral blood. The mean presented is from three to four experiments (* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$, Student's t test).

TABLE 1

Baseline Characteristics

EBER	PD-L1	Stage	Number of prior therapies	Genomic alterations identified	Tumor mutation burden
Patient no. 1, 21 year-old male					
–	+	IVB	ABVD ×7 cycles – PD ESHAP ×3 – PR BEAM followed by PBSCT Irradiation (3,060 cGy), sternum and parasternal areas - PR for 2 months Brentuximab ×8 – PD IGEV ×3 - CR for 6 months COPP ×2 with irradiation – PD Irradiation (20 Gy in 5 days), L2 and left iliac crest Nivolumab - CR in 2 months	Not done	Not done
Patient no. 2, 34-year-old male					
+	+	III	ABVD ×4, ABV ×2 - CR for 1 year ICE ×3 – CR BEAM with PBSCT - CR for 7 months Brentuximab ×4 – PD Irradiation (36 Gy in 20 fractions) Nivolumab - CR in 6 months	<i>STAT6</i> Q286R mutation	<30% purity
Patient no. 3, 23-year-old male					
–	+	II	ABVD ×4 – PD Brentuximab ×3 – PD ICE + brentuximab ×2 – PD Nivolumab (2 doses) and concurrent irradiation (total 40 Gy in 20 fractions, mediastinal nodes)	<i>ERBB2</i> amplification	Intermediate, 8.15 mutations per megabase

Abbreviations: EBER = Epstein-Barr virus-encoded small RNA; PD-L1 = programmed cell death-ligand 1; ABVD = adriamycin, bleomycin, vinblastine and decarbazine; PD = programmed cell death; ESHAP = etoposide, methylprednisolone, cytarabine and cisplatin; PR = partial remission; BEAM = BCNU, etoposide, cytarabine, melphalan; PBSCT = peripheral blood stem cell transplant; IGEV = ifosfamide, gemcitabine, etoposide and vincristine; CR = complete response; COPP = cyclophosphamide, vincristine, procarbazine and prednisone; ERBB2 = Erb-B2 receptor tyrosine kinase 2; ICE = ifosfamide, carboplatin and etoposide.