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Safety and Long-Term Efficacy of Pembrolizumab Plus a Personal Dendritic Cell Vaccine in a Patient with Metastatic Melanoma

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ABSTRACT

Background: *Monoclonal antibodies that target programmed-death molecule-1 (anti-PD-1) are an effective immunotherapy for advanced melanoma. A promising investigational approach is a patient-specific therapeutic vaccine consisting of autologous dendritic cells pulsed with autologous tumor antigens from autologous tumor cells that are self-renewing in tissue culture. There is a strong rationale for combining these two immunotherapy approaches.*

Patient and Methods: *A 72-year-old White female was diagnosed with stage IVb metastatic melanoma confirmed by biopsies of lung and soft-tissue nodules. A short-term cell line was established from a 1.6 cm lung nodule. Autologous dendritic cells were differentiated from autologous monocytes obtained via leukapheresis. Per protocol, treatment was initiated with intravenous pembrolizumab every three weeks while the personal vaccine was manufactured. During the next 24 weeks, she received eight subcutaneous vaccine injections and eight more pembrolizumab infusions. After completing concurrent therapy, she continued pembrolizumab for an additional 27 months before stopping because of post-injection pruritus.*

Results: *Treatment was well-tolerated, both during the nine weeks of single-agent pembrolizumab as well as during the six months of concurrent immunotherapy. Just before starting the combined therapy, radiologic tests confirmed an objective partial response. Subsequently, her measurable disease continued to improve with SUV intensity decreased on PET scans and tumor size decreased on CT scans. One year after completing the vaccine, PET/CT scans were interpreted as showing a complete remission which was still ongoing 30 months later, 3.5 years after the initial diagnosis.*

Conclusions: *This personalized combination immunotherapy treatment is encouraging based on the lack of toxicity, confirmation of anti-tumor efficacy, and observed long-term disease control. Additional investigation of this combination is warranted.*

Keywords

Anti-PD-1, Autologous tumor antigens, Dendritic cell vaccine, Metastatic melanoma.

Background and Rationale

The introduction of monoclonal antibody checkpoint inhibitors has revolutionized the treatment of metastatic melanoma. The first checkpoint inhibitor that received regulatory approval was the anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) monoclonal antibody ipilimumab in 2010 [1]. Subsequently, in 2014, nivolumab and pembrolizumab were approved as the first two monoclonal antibodies that bind programmed death molecule-1 (PD-1) [2,3]. In a randomized comparison, pembrolizumab was associated with less toxicity and produced a higher objective response rate than ipilimumab [4]. In a large randomized trial that enrolled young patients (mean age 59 years) with high-

performance status (75% ECOG score of 0), the combination of nivolumab and ipilimumab was associated with a higher objective response rate than nivolumab or ipilimumab alone [5], a higher 3-year progression-free survival (PFS) rate [6], and a higher 5-year overall survival rate [7]. Unfortunately, the combination was associated with a 60% rate of severe to life-threatening toxicity, mostly immune-related adverse events (IRAE), compared to rates of about 15% for single agents [5,6]. For this reason, in clinical practice, many oncologists reserve the combination for only their youngest and healthiest patients and use single-agent anti-PD-1 for elderly patients and younger patients with significant co-morbidities. It would be desirable to add additional therapies to anti-PD-1 antibodies with the goal of increasing response rates and survival without increasing toxicity.

A promising anti-cancer immunotherapy is a patient-specific, personal, therapeutic vaccine consisting of autologous dendritic cells (DC) loaded with autologous tumor antigens (ATA) derived from a short-term cell line of autologous self-renewing cancer cells [8]. Before the introduction of the checkpoint inhibitors, DC-ATA was associated with a 5-year survival rate of 50% in a 54-patient single-arm trial in patients with advanced melanoma [9]. Subsequently, a small randomized trial demonstrated that DC-ATA was associated with better survival and a more desirable immune response compared to injections of a vaccine consisting of autologous irradiated proliferating cancer cells [10-12]. This included a patient with stage IVc widespread metastatic melanoma that was refractory to all therapies available at that time, who experienced a complete remission that was ongoing five years after starting the vaccine [13]. Testing of similar DC-ATA vaccines has yielded encouraging results in patients with renal cell cancer [14], hepatocellular cancer [15], ovarian cancer [16] and glioblastoma [17,18].

The mechanism of action of anti-PD-1 checkpoint inhibitors is blocking inhibition of previously existing anti-tumor immune responses by the interaction of PD-1 and anti-programmed death molecule ligand-1 (PDL-1) on cytotoxic T cells and tumor cells, respectively [19]. A vaccine such as DC-ATA may induce immune responses to additional tumor-associated antigens, or induce first-time immune responses in immunologically "cold" tumors, or enhance immune responses to such antigens, and thus potential increase the benefit of anti-PD-1 therapy [20,21]. However, it is possible that injecting such a vaccine could result in an increased frequency of IRAE; therefore, the first step is to assure the safety of the combination with no decrease in efficacy.

Patient and Methods

An asymptomatic 72-year-old White female of Dutch ancestry was found to have new bilateral non-calcified lung nodules detected on a routine surveillance computerized tomography (CT) scan; one nodule was greater than 1 cm in diameter. A combined positron emission tomography/computerized tomography scan (PET/CT) showed a 1.4 cm left upper lobe nodule with a standardized uptake value (SUV) of 8.3, a 1.5 cm subcutaneous nodule with SUV 30.4 over the right scapula, and small hypermetabolic nodules near the right kidney and near bowel. Hematologic and chemistry laboratory studies were all within normal limits, including the serum lactate dehydrogenase level. Biopsies of lung and subcutaneous nodules both showed metastatic melanoma. She was staged as IVb. There was no primary melanoma detected and no history of a previous melanoma. Additional testing showed that the tumor was positive for *BRAF V600K* and *TERT* mutations and had a high tumor mutation burden. PD-L1 could not be determined due to heavy melanin staining. Her mother and maternal uncle both had ocular melanoma, and a maternal aunt had cutaneous melanoma. One laboratory detected an *ataxia-telangiectasia mutation* (*ATM*) but no known pathogenic mutations were identified in the *ATM* gene.

She enrolled in a single-institution safety trial of anti-PD-1 plus AV-MEL-1 (NCT03743298). Details regarding the manufacturing of DC-ATA such as AV-MEL-1 have been published previously [3,18]. The left upper lobe nodule, which was 1.6 cm in diameter at the time of resection, was submitted to AIVITA Biomedical Inc. (Irvine, CA.) where the tumor was processed into a cell suspension, and a short-term cell line was established. After 24 days of cell culture, there were more than one million cancer cells. Nine days after surgery, she underwent a leukapheresis that yielded 1.76 trillion monocytes from which DCs were differentiated during six days of incubation with interleukin-4 and granulocyte-macrophage colony-stimulating factor (GM-CSF). Seven days after the leukapheresis (16 days after the lung wedge resection), she started treatment with pembrolizumab 200 mg i.v. every three weeks. Her personal DC-ATA vaccine was manufactured and passed quality assurance testing during the nine weeks while she received the first four pembrolizumab infusions. Over six days, autologous DC were differentiated from the autologous monocytes collected during the leukapheresis. Overnight incubation of DC with the lysate of 3.35 million cancer cells resulted in doses of 20 million DC-ATA cells that were cryopreserved in liquid nitrogen. At the time of each treatment, individual doses were shipped to the treatment site where a vaccine vial was thawed and suspended in 500 microgram of GM-CSF. As in previous DC-ATA trials, the eight subcutaneous injections were administered at weeks 1,2,3,8,12,16,20, and 24. There were no adverse events (AE) reported during this period. She received eight more pembrolizumab infusions during the 24 weeks of vaccination, three of which were administered on the same day as a vaccine injection. After completing concurrent therapy, she continued pembrolizumab for an additional 27 months.

Results

All doses were delivered as planned and treatment was well-tolerated. There were no IRAE, or other AE or significant laboratory abnormalities reported during the initial nine weeks of single-agent pembrolizumab, nor during the 24 weeks of concurrent immunotherapy. More than two years after completing the vaccine injections, she eventually developed a generalized rash and pruritus in association with pembrolizumab injections which led her to request discontinuing therapy. The rash and pruritus resolved during treatment with topical corticosteroids (1% Kenalog cream) and did not persist or recur after pembrolizumab was discontinued.

In the week before starting AV-MEL-1, radiologic tests confirmed an objective partial response of the remaining metastases. CT showed a diminished left paratracheal lymph node, diminished posterior right shoulder subcutaneous nodule, and resolution of the soft tissue nodule posterior to the right kidney. During concurrent treatment, her detectable disease continued to improve with SUV intensity decreased on PET scans and tumor size decreased on CT scans. One year after completing the vaccine, PET/CT scans were interpreted as showing a complete remission, which was still ongoing 30 months later, 3.5 years after the initial diagnosis.

Discussion

The most important observation in this report is the lack of toxicity associated with concurrent administration of the anti-PD-1 monoclonal antibody pembrolizumab with a personal DC-ATA vaccine, AV-MEL-1. That this patient experienced no AE in association with her first three pembrolizumab infusions is not surprising. In a randomized trial in patients with unresectable regional or distant metastatic melanoma who had been treated with no more than one prior therapy [5], the most frequent AEs of any grade associated with every three-week pembrolizumab infusions in 277 patients were fatigue 19%, diarrhea 14%, pruritus 14%, and rash 13%; Grade 3 or 4 AEs were experienced by 10%. The most frequent IRAE was hypothyroidism (9%). In another randomized trial, in which 316 patients with unresectable previously untreated regional or distant metastatic melanoma were treated with the anti-PD-1 nivolumab [4], 82% experienced an AE, 16% grade 3 or 4 AE, and 8% discontinued anti-PD-1 because of an AE. Historically, no melanoma patients treated with DC-ATA experienced Grade 4 AEs or discontinued treatment because of toxicity [9-11]. Grade 3 AEs were reported in less than 2%. However, the majority of patients who received multiple DC-ATA injections reported mild local injection site reactions, including discomfort and erythema or flu-like symptoms [8]. AEs resolved rapidly without medical intervention. It is reassuring and encouraging that no AEs were reported while AV-MEL-1 was being administered concurrently with pembrolizumab. Since this patient was treated, two additional patients with metastatic melanoma have completed eight AV-MEL-1 injections concurrently with pembrolizumab without significant toxicity.

The other noteworthy observation in this report is the eventual complete remission and long-term control of distant metastatic melanoma. That this patient had a complete response by PET/CT scan and was still progression-free 3.5 years after a diagnosis of metastatic melanoma is atypical for patients treated with single-agent anti-PD-1 [4-7]. The objective response rate for every three-week pembrolizumab was 33%, the complete response rate was only 6%, and the median progression-free survival rate was only 5.5 months [4]. The objective response rate for every two-week nivolumab was 44%, the complete response rate 9%, and the median progression-free survival 6.9 months [5].

Even though this patient had distant metastatic melanoma at diagnosis, she had several clinical features that are associated with better responses to immunotherapy. These include the high tumor mutation burden, the relatively small tumor burden, the lack of visceral metastases other than lung, no prior history of cutaneous melanoma, and no previous systemic melanoma treatment. There is some suggestion that asymptomatic patients who present with melanoma metastatic to lung have a better prognosis compared to other stage 4 presentations [22]. Even before checkpoint inhibitor therapy became available, the senior author used DC-ATA to treat two patients initially diagnosed with lung metastases without a prior history of cutaneous melanoma, who have survived more than 10 years despite other visceral metastases [9].

This is the first report of treatment with the combination of anti-PD-1 in combination with a DC vaccine loaded with antigens from an autologous short-term cell line. However, others are also testing the combination of anti-PD-1 with personal vaccines that target patient-specific neoantigens. In patients with surgically resected locally advanced melanoma, a 157-patient randomized trial of adjuvant therapy showed a recurrence-free survival benefit for a vaccine plus anti-PD-1 combination versus anti-PD-1 alone [23]. The anti-PD-1 antibody was pembrolizumab in both arms. The vaccine in that trial was mRNA-4157, an mRNA neoantigen vaccine that encodes up to 34 neoantigens. Serious AEs attributed to treatment were observed in 14% of patients in the combined therapy arm and 10% in the pembrolizumab arm. IRAEs of any grade were recorded in 36% of patients in both groups. Most IRAEs were grade 1–2; higher grade IRAEs were noted in 11% of patients in the combined therapy arm and 14% in the pembrolizumab arm. AEs led to discontinuing pembrolizumab in 25% of patients in the combined therapy arm compared to 18% in the pembrolizumab arm. Based on experience with mRNA and DC anti-Covid vaccines, toxicity appears greater for the mRNA vaccine compared to DC vaccines [24]. From a platform perspective, vaccines consisting of DC loaded with antigens *ex vivo* may be more effective and less toxic than direct injection of antigens or *in vivo* antigen production by mRNA or DNA vaccines for both cancer and infectious diseases [11,24,25].

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References

1. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010; 363: 711-723.
2. Topalian SL, Sznol M, McDermott DF, et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. J Clin Oncol. 2014; 32: 1020-1030.
3. Hamid O, Robert C, Daud A, et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. N Engl J Med. 2013; 369: 134-144.
4. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med. 2015; 372: 2521-2532.

5. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med. 2015; 373: 23-34.
6. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med. 2017; 377: 1345-1356.
7. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med. 2019; 381: 1535-1546.
8. Dillman RO, Nistor GI, Keirstead HS. Autologous dendritic cells loaded with antigens from self-renewing autologous tumor cells as patient-specific therapeutic cancer vaccines. Hum Vaccin Immunother. 2023; 19: 2198467.
9. Dillman RO, Selvan SR, Schiltz PM, et al. Phase II trial of dendritic cells loaded with antigens from self-renewing, proliferating autologous tumor cells as patient-specific antitumor vaccines in patients with metastatic melanoma: final report. Cancer Biother Radiopharm. 2009; 24: 311-319.
10. Dillman RO, Cornforth AN, Depriest C, et al. Tumor stem cell antigens as consolidative active specific immunotherapy: a randomized phase II trial of dendritic cells versus tumor cells in patients with metastatic melanoma. J Immunother. 2012; 35: 641-649.
11. Dillman RO, Cornforth AN, Nistor GI, et al. Randomized phase II trial of autologous dendritic cell vaccines versus autologous tumor cell vaccines in metastatic melanoma: 5-year follow up and additional analyses. J Immunother Cancer. 2018; 6: 19.
12. Nistor GI, Dillman RO. Cytokine network analysis of immune responses before and after autologous dendritic cell and tumor cell vaccine immunotherapies in a randomized trial. J Transl Med. 2020; 18: 176.
13. Dillman RO, Nistor GI, Poole AJ. Genomic, proteomic, and immunologic associations with a durable complete remission of measurable metastatic melanoma induced by a patient-specific dendritic cell vaccine. Hum Vaccin Immunother. 2020; 16: 742-755.
14. Dillman RO, Depriest C. Dendritic cell vaccines presenting autologous tumor antigens from self-renewing cancer cells in metastatic renal cell cancer. J Exploratory Res Pharmacol 2018; 3: 93-101.
15. Wang X, Bayer ME, Chen X, et al. Phase I trial of active specific immunotherapy with autologous dendritic cells pulsed with autologous irradiated tumor stem cells in hepatitis B-positive patients with hepatocellular carcinoma. J Surg Oncol. 2015; 111: 862-867.
16. Corr B, Abaid LN, Mason JR, et al. Randomized phase 2 trial of personal dendritic cell (DC) autologous tumor antigen (ATA) vaccines in newly diagnosed advanced ovary cancer. Gynecologic Cancer. 2023.
17. Piccioni DE, Duma CM, Kesari S, et al. Progression free survival in a phase 2 trial of personal dendritic cell vaccines in patients with newly diagnosed glioblastoma. J Clin Oncol Res Ther. 2022; 7: 10149.
18. Bota DA, Taylor TH, Piccioni DE, et al. Phase 2 study of AV-GBM-1 (a tumor-initiating cell targeted dendritic cell vaccine) in newly diagnosed Glioblastoma patients: safety and efficacy assessment. J Exp Clin Cancer Res. 2022; 41: 344.
19. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012; 12: 252-264.
20. Dillman RO. An update on the relevance of vaccine research for the treatment of metastatic melanoma. Melanoma Manag. 2017; 4: 203-215.
21. Schlom J, Gulley JL. Vaccines as an integral component of cancer immunotherapy. JAMA. 2018; 320: 2195-2196.
22. Leung AM, Hari DM, Morton DL. Surgery for distant melanoma metastasis. Cancer J. 2012; 18: 176-184.
23. Weber JS, Carlino MS, Khattak A, et al. Individualised neoantigen therapy mRNA-4157 (V940) plus pembrolizumab versus pembrolizumab monotherapy in resected melanoma (KEYNOTE-942): a randomised, phase 2b study. Lancet. 2024; 403: 632-644.
24. Nistor GI, Dillman RO, Robles RM, et al. A personal COVID-19 dendritic cell vaccine made at point-of-care: Feasibility, safety, and antigen-specific cellular immune responses. Hum Vaccin Immunother. 2022; 18: 2100189.
25. Dillman RO, Nistor GI, Jonny J, et al. Prevention of symptomatic Covid-19 infection by personal dendritic cell vaccine. J Vaccin Immuno Immunopathol. 2023; 8: 189.