Treatment of Metastatic Melanoma in an Immunodeficient Patient

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ABSTRACT

Melanoma is the leading cause of mortality in skin cancers. Individuals with inflammatory bowel disease have a higher risk of developing melanoma. When first line surgical intervention is not effective or indicated, adjuvant treatments such as rose bengal (PV-10) injection can be used. Immunodeficient patients may not exhibit ideal responses to such therapeutics. This case describes the course of melanoma treatment in a patient with the comorbid condition of Crohn’s disease. A 75-year old Caucasian woman with a past medical history of Crohn’s disease presented to the surgical oncology clinic with a hyperpigmented, previously hemorrhaging lesion on her left lower extremity. A biopsy of the lesion was performed and pathology results revealed melanoma. The patient underwent a wide local excision of the tumor with skin graft and sentinel lymph node biopsy. Post-surgical pathology revealed presence of metastatic disease in the left groin. Chemotherapy and an isolated limb infusion (ILI) were contraindicated due to the unhealed skin graft from the original excision. As an alternative to chemotherapy or ILI, PV-10 intral esional injections were administered without clinical response. After the skin graft healed, an ILI with left groin lymph node dissection was performed. The patient was stable at post-operative follow up.

The basis for a majority of novel adjuvant treatments for melanoma is utilization of the host immune response. Based on the clinical findings of this case, it can be observed that the host immune response may be essential for complete response of PV-10 injections. This case supports further study on a mechanistic level of these novel treatments. With new data in this regard, targeted therapies may be of future use to provide best treatment outcomes for patients.

INTRODUCTION

Melanoma is the leading cause of mortality in skin cancers; it is associated with greater morbidity and mortality than nonmelanoma skin cancers.1,2 Its prognosis is highly correlated to depth of invasion, with deeper tumors negatively impacting 10-year survival.3 First-line treatment involves surgical excision of the tumor, potentially followed by chemotherapy or radiation. Melanoma tumor growth is highly dependent on an immunosuppressed state.4 These cancer cells induce immunosuppression through a variety of mechanisms, including mutations...
within malignant cells, secretion of immunosuppressive cytokines, and induction of tolerance.\textsuperscript{3} In melanoma, regulatory CD4+CD25+ T cells express \textit{FOXP3} and secrete immunosuppressive cytokines, which suppress the antitumor immune response. There is also much interplay between dendritic cells and cytokines, such as transforming growth factor-\(\beta\) and interleukin (IL)-10. All of these factors contribute to the immunosuppressed microenvironment.\textsuperscript{4}

Some immunocompromised states, such as in transplant recipients and HIV/AIDS patients, have been associated with a higher risk of melanoma.\textsuperscript{4} Iatrogenic immunosuppression induced by medications for treatment of diseases such as Crohn’s disease is of special consideration. Different medications induce immunosuppression via varying mechanisms. For example, prednisone inhibits T cell proliferation against antigens, while azathioprine inhibits nucleotide synthesis, thereby inhibiting proliferation of B and T effector cells.\textsuperscript{4}

The role of Crohn’s disease and the medication used to treat it in the development of melanoma is uncertain. However, an increased risk of melanoma in Crohn’s patients has been established.\textsuperscript{1}

### CASE PRESENTATION

A 75-year-old Caucasian woman presented to surgical oncology clinic with a hyperpigmented lesion with a history of bleeding on her left lower extremity. Her past medical history included atrial fibrillation, Crohn’s disease, and well-controlled diabetes. She denied family or personal history of skin cancer, but stated she had a great deal of sun exposure for approximately 2 years during her early 20s. She had a 15-year 3 pack per day smoking history but quit over 40 years ago. Medications included budesonide, natalizumab, mesalazine, sotalol, pravastatin, aspirin, insulin, cyanocobalamin, and a previous history of prednisone use. She was not taking prednisone at the time of presentation. The patient reported allergies to azathioprine and mercaptopurine with reactions of aphagia and stiffness, respectively. Past surgical history included thymectomy via sternotomy for thymoma, total abdominal hysterectomy with a laparoscopic bilateral salpingoopherectomy, and repaired umbilical hernia. Physical exam was unremarkable aside from the lesion of the anterior left lower extremity. She was clinically node negative.

A biopsy of the lesion was performed. Results were consistent with a diagnosis of a melanoma 7.0 mm in depth with ulceration present, two findings that are associated with unfavorable prognosis.\textsuperscript{3} As genetic analysis reported the tumor BRAF V600 negative, she was not a candidate for BRAF inhibitor therapy, which down-regulates signal transduction of the mutated gene. The patient then underwent a radical wide excision of the left lower extremity with skin graft and sentinel lymph node biopsy of the left groin. Satellite nodules were noted and biopsied during surgery. Pathology revealed foci of metastatic melanoma as well as metastases present in the sentinel lymph node.

The patient was not deemed a candidate for chemotherapy or isolated limb infusion (ILI) until her skin graft healed. The patient received rose bengal (PV-10) injections for local metastasis. One lesion was selected for injection, and another was selected as a control. The patient initially had a partial response and 4 more lesions were injected. After the additional injections, new lesions developed in the distal limb, but were confined to the treated area of the left leg. The increase in regional disease deemed her non-responsive to this treatment.

An ILI with left inguinal dissection was per-
formed for the extensive in-transit disease. The limb infusion involved delivering high dose chemotherapy through minimally invasive, intra-arterial catheters. An extremity tourniquet isolated the left lower limb from the body in order to avoid serious side effects associated with systemic chemotherapy. After the procedure, the patient presented with stable post-operative examination. Figures 1 and 2 depict the lesions observed after completion of treatments at last follow up. A clinical impression of disease state could not be determined, as the necessary time frame for the isolated limb infusion effects had not elapsed. Table 1 outlines the course of treatment in weeks.

DISCUSSION

Malignant melanoma is the leading cause of death in skin disease with continuously increasing mortality rates. Individuals with inflammatory bowel disease, such as Crohn’s disease and ulcerative colitis, are at a 37% greater risk of developing melanoma; those with Crohn’s disease have the highest risk according to a study by Singh et al. In North America alone, as many as 630,000 suffer from Crohn’s disease, with 57,000 people diagnosed each year. Considering the high melanoma mortality rate, identifying consequences of immunosuppressive therapy and targeted treatment for this subset of patients is of interest.

This increased risk has been attributed to genetic factors that may alter the host’s ability to produce an immune response. Immunosuppressive agents, such as corticosteroids and thiopurines, used to manage these disorders may render the individual immunocompromised. Although these patients have an additional facet of their disease, management of these cases parallels those of immunocompetent patients. When first line surgical treatment is insufficient in eradicating the cancer, there are a variety of adjuvant treatment options, many of which involve immunomodulating mechanisms. These immunotherapy treatments have limited data from clinical trials in regard to their efficacy and safety.

One treatment currently under study is the use of rose bengal, a dye previously used to monitor liver function. PV-10 is an injectable 10% rose

Figure 1. Anterior view of left extremity with numerous melanoma lesions after PV-10 injections and 2 weeks post-isolated limb infusion. Skin graft also visible from original excision.

Figure 2. Lateral view of left extremity.

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**Table 1:** Course of Treatment in Weeks

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bengal solution currently under evaluation for treatment of melanoma.\textsuperscript{9} The specific mechanism of PV-10 is yet to be completely understood; however, it has been observed in murine studies to accumulate within neoplastic cell lysosomes, leading to autolysis. According to a study conducted by Agarwala et al.,\textsuperscript{10} there was also minimal toxicity in normal tissue with selective chemoablation of injected tumors. Another study conducted by the same investigators demonstrated a “by-stander” effect, in which uninjected lesions were also found to have resolved.\textsuperscript{11} This is a particularly unique aspect of this therapy since it supports the concept of an underlying immunologic response. Although the main effect is tumor ablation, it appears to subsequently reduce tumor burden and expose tumor antigens to the host immune system. This dual activity is of great significance given that it could have systemic benefits leading to a reduction in morbidity as well as rate of recurrence.\textsuperscript{10,11}

This patient presented with advanced stage metastatic melanoma complicated by inflammatory bowel disease, which limited her options for systemic immunotherapy. Her tumor was BRAF negative, and she was opposed to chemotherapy, further narrowing the scope of possible treatment. The skin graft also delayed her eligibility for isolated limb infusion and chemotherapy for approximately 5 months. Delaying treatment was not preferred due to the advanced stage of her cancer. Given this clinical picture, the patient was informed of her treatment options and decided to have the PV-10 injections. In a study of 28 patients, 71% responded to PV-1-0 injections, with 50% showing complete response.\textsuperscript{11} Her non-responsiveness to the PV-10 injections could be partially attributed to her immune deficient state, as melanosomas in immunocompromised patients tend to be more aggressive in nature.\textsuperscript{4}

A correlation has been established between host response and melanoma disease state. Low levels of melanoma-specific antibodies are associated with metastatic melanoma, while high titers of these antibodies are correlated with local tumors.\textsuperscript{12} This concept highlights the importance of the immune response in treating melanoma. Evidence-based treatment planning for melanoma is limited in the care of immunosuppressed patients.\textsuperscript{4} Since melanoma is more common and behaves more aggressively in immunodeficient patients,\textsuperscript{4} additional consideration

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<th>9</th>
<th>10</th>
<th>11</th>
<th>14</th>
<th>18</th>
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<tr>
<td>Treatment</td>
<td>Biopsy of original single lesion</td>
<td>Local wide excision with sentinel node biopsy</td>
<td>Follow up: rapidly progressing skin lesions</td>
<td>First administration of PV-10 injections</td>
<td>Injected lesion biopsies. PET scan negative for distant metastasis</td>
<td>4 more PV-10 injections</td>
<td>Follow up</td>
<td>Isolated limb infusion procedure</td>
<td>Follow up</td>
</tr>
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*Table 1. Melanoma Treatment Timeline*
should be given in deciding treatment. Based on the findings of this case, PV-10 injections are of limited benefit to this patient population due to a diminished immune response. The mechanism of action for the PV-10 injections should be studied to further support this observation. Other treatments that differ in mechanism, such as cytotoxic agents, may have a stronger impact on eliminating neoplastic cells or preventing distant disease in this patient population. This case supports the need for further studies exploring targeted therapies for melanoma patients, particularly those with immunosuppressive disease or treatment.

LEARNING POINTS

• The clinical result of PV-10 injection may be dependent on host immunological response.

• Treatments other than PV-10 injections may be preferred in immunocompromised patients.

• Further investigation of the mechanism of PV-10 response, as well as targeted therapies for immunocompromised individuals, is needed.

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REFERENCES


