Treatment of melanoma in-transit metastases with combination intralesional interleukin-2, topical imiquimod, and tretinoin 0.1% cream

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INTRODUCTION

The treatment of in-transit and satellite melanoma metastases is challenging. Treatment options for these cutaneous and subcutaneous lesions include surgical excision, radiotherapy, isolated limb infusion/perfusion, electrochemotherapy, cryotherapy, laser therapy (pulsed dye or carbon dioxide), systemic treatment with interferon-α or interleukin-2 (IL-2), topical imiquimod, dinitrochlorobenzene, and intralesional immunotherapy with bacillus Calmette-Guérin vaccine, granulocyte macrophage colony-stimulating factor, IL-2, or talimogene laherparepvec.[1] Response rates for these therapies are often suboptimal. Topical imiquimod has been used for the treatment of both melanoma in situ (in patients who are either poor surgical candidates or have positive margins after excision) and in-transit metastases.[1,2] There are reports of regression of locoregional melanoma metastases after topical imiquimod to cutaneous lesions.[1,2] Combination therapy using intralesional IL-2 together with topical imiquimod and tretinoin may increase the efficacy of IL-2.[3] Here we report the case of a patient with in-transit metastatic melanoma treated with intratumoral IL-2 together with topical imiquimod and tretinoin cream.

Abbreviation used:

IL-2: interleukin-2

CASE REPORT

A 64-year-old man with a history of Crohn's disease and depression presented with a 1.2-cm enlarging black nodule involving his right ear. A biopsy found melanoma with a Breslow depth of 2 mm without mitoses or vascular invasion. He underwent excision with 2-cm margins and sentinel lymph node biopsy, and the result of the latter was negative. Eight months later, the patient had a local recurrence and underwent right ear amputation and a second sentinel lymph node biopsy that found 1 positive lymph node. He was evaluated for systemic therapy, but his active Crohn's disease precluded him from immunotherapy with ipilimumab, treatment with high-dose IL-2 was contraindicated given his history of depression with suicidal ideation, and the tumor did not have a BRAF mutation. The patient had recurrent disease in the auditory canal 3 months later and was treated with local radiation followed by wide excision and lymph node dissection (all lymph nodes negative). In-transit metastases developed adjacent to the right ear surgical scar, and the patient underwent 5 cycles of chemotherapy with carboplatin and paclitaxel. The in-transit metastases decreased in size and number over the next 3 months; 9 months later, however, more than 10 new in-transit metastases were noted at the periphery of the right ear graft site (Fig 1, *A*).

The patient was treated with intralesional high-dose IL-2 twice weekly (beginning at 7 million units per treatment and increased by 2 million units weekly) in conjunction with topical imiquimod and tretinoin 0.1% cream applied together once daily to all visible metastases with a 5-cm peripheral margin. Treatment side effects were tolerable and included

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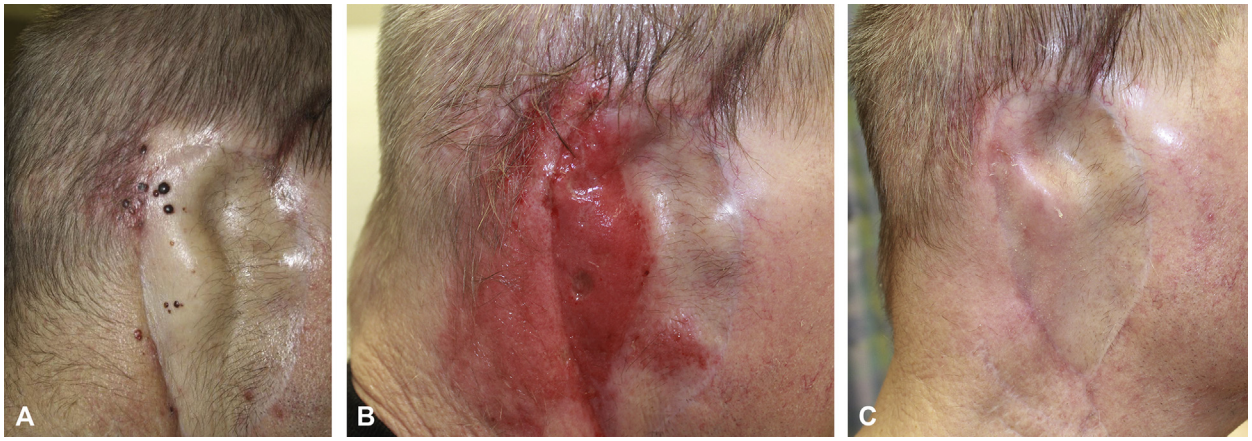

Fig 1. **A**, Melanoma in-transit metastases at the periphery of the right ear graft. **B**, Inflammatory response after 2 weeks of treatment (4 injections of intralesional IL-2 plus topical imiquimod and tretinoin 0.1% cream applied once daily). **C**, Clinical resolution of the in-transit metastases 2 months after treatment and with maintenance therapy (topical imiquimod with tretinoin 0.1% cream daily for 7 consecutive days monthly).

transient chills, nausea (controlled with ondansetron), and local inflammatory response. Skin erosions and intense erythema were visible after 2 weeks of treatment (4 injections; Fig 1, *B*), and it was decided to maintain the dose of IL-2 at 11 million units per injection. After 5 weeks (10 injections), there was complete resolution of all visible in-transit metastases, and intralesional immunotherapy was stopped. The patient was then maintained on topical imiquimod and tretinoin 0.1% cream applied once daily for 7 consecutive days each month (Fig 1, *C*). Two months later, there was no clinical evidence of skin disease, and a positron emission tomography scan was negative for metastatic disease. Nine months after treatment, the skin remained clear, but the patient noted lower back pain and was found to have bony metastases and liver and pulmonary metastases. A biopsy of the sacrum confirmed metastatic melanoma. The patient elected comfort care and died 10 months after completion of therapy with intralesional IL-2.

DISCUSSION

Intralesional IL-2 may be beneficial for the treatment of in-transit melanoma metastases.[3-5] Earlier studies used lower concentrations (3 and 3.6 million units) with lower response rates (50% and 62.5%) compared with the more recent study by Shi et al[3] in which higher-dose IL-2 (up to 22 million units) combined with topical imiquimod and tretinoin 0.1% cream resulted in a 100% complete response.[3-5] Our case was included as a data point in the larger series by Shi et al[3] that was published previously and highlights the efficacy and tolerability of this therapeutic regimen. For our patient, we planned to titrate up from 7 to 22 million units per injection, but in the setting of a robust inflammatory response, therapy was maintained at 11 million units per injection. After 5 weeks of therapy, there was no evidence of residual disease, so maintenance therapy was started. As highlighted in the recent publication by Shi et al,[3] 11 of 11 patients (including our case) were treated with 4 to 6 weeks of combination therapy and achieved complete clinical response within 1 to 3 months.[3] Our patient was categorized as having smaller lesion size (<1 cm) compared with other cases (7 of 11 patients had >1-cm lesions) and medium number of total lesions (between 6 and 19) compared with other cases (5 of 11 patients had >20 lesions).[3] Overall, the size and number of metastatic lesions had no effect on the clinical response.[3]

Each agent of the triple regimen has a distinct mechanism. IL-2 may induce antitumoral response via both activation of natural killer cells and CD8 and CD4 T cells.[6] Imiquimod induces antitumoral cytokines including tumor necrosis factor, interferon-α, and interleukin-12 via interaction with toll-like receptors 7 and 8.[7] Topical retinoids influence keratinocyte maturation and may increase epidermal penetration of imiquimod, resulting in an enhanced inflammatory response.[8] A randomized study of 90 patients with lentigo maligna found an increased likelihood of achieving a robust inflammatory response with combination tazarotene gel and imiquimod cream (80%) versus imiquimod cream alone (60%).[8]

Although new targeted therapies have revolutionized the way advanced melanoma is treated, intralesional immunotherapy may have a role in treating patients with multiple comorbidities and poor

functional status and patients with contraindications to systemic immunotherapy or who have not responded to targeted therapy or chemotherapy. Intralesional IL-2 is also appealing for the management of patients with disease limited to in-transit metastases or local recurrences. Mid- to high-dose intralesional IL-2 combined with topical imiquimod and tretinoin cream should be considered for the management of cutaneous melanoma metastases.

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