Topical imiquimod in combination with brachytherapy for unresectable cutaneous melanoma scalp metastases

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INTRODUCTION

Scalp melanomas are associated with poor disease-related and survival outcomes compared with melanomas affecting other anatomical sites, partially due to high rates of in-transit metastases (ITM), defined as localized >2 cm from the primary tumor but not beyond draining lymph nodes.[1,2] The standard treatment for ITMs is surgical excision[3]; however, surgery is often impractical for multiple or diffuse ITMs. Currently, the only Food and Drug Administration-approved therapy, specifically directed at ITMs is talimogene laherparepvec, an injectable modified oncolytic herpes simplex virus, which has shown modest response rates in phase III studies in patients with locally advanced melanoma.[4] Local therapies (intra-arterial regional perfusion, intralesional interleukin-2, Bacille Calmette-Guerin vaccination, diphencyprone, carbon dioxide laser, electrochemotherapy) have also been tried with varying degrees of success.[5,6]

One local therapy is topical imiquimod, an immunomodulator which binds to toll-like receptor 7 stimulating tumor-specific T cell responses.[7] Imiquimod has already been found to be safe and effective in treating cutaneous malignancies such as lentigo maligna.[8] Recent guidelines recommend topical imiquimod application for 10 to 14 weeks,[9] with individualized regimens tailored based on clinical reactions.

Abbreviation used:

ITM: in-transit metastases

Aside from local therapies, radiation has been used for palliative or adjuvant therapy in advanced cutaneous malignant melanoma. A retrospective study on palliative external beam radiotherapy in stage III melanoma patients, half with ITMs, demonstrated a complete response of 44% at 3 months.[10] Compared with conventional external beam radiotherapy, brachytherapy is short-range radiation delivered via sources placed within or close to the target, which has already been used to treat cutaneous and hematologic malignancies.[11] An important advantage of brachytherapy is the ability to match radiation dose to the curvature of complex surfaces like the scalp, achieving a more homogeneous dose throughout the target and minimizing injury to adjacent normal tissue, and over a curvaceous surface, is much more conformal than standard electron beam therapy.

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All patients gave consent for their photographs and medical information to be published in print and online and with the understanding that this information may be publicly available.

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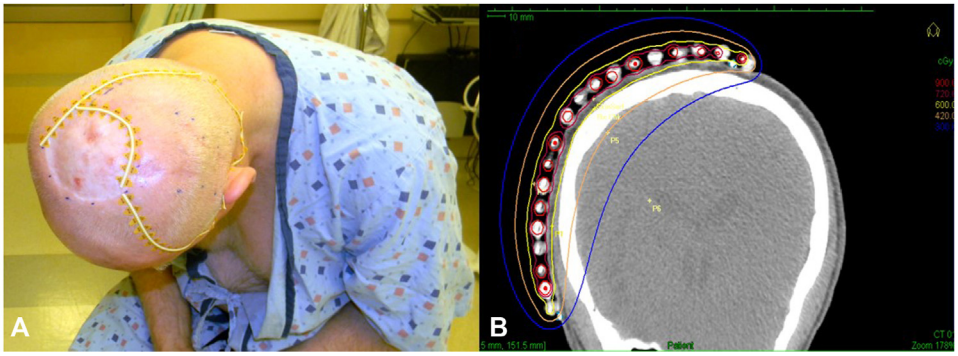

Fig 1. Clinical mapping and radiation dose distribution. **A,** Clinical target area outlined with copper wire. **B,** The *yellow isodose line* represents a highly conformal 100% of the dose (6 *Gray* ×5).

Mounting evidence suggests that radiation can stimulate antitumor immune responses, thereby mediating a response distant from the irradiated volume (abscopal effect); thus, leading to regression of not only the treated tumor but also untreated metastases at other locations.[12] Here, we describe 3 patients with surgically unresectable scalp ITMs who experienced complete responses with brachytherapy followed by topical imiquimod.

REPORT OF CASES

Case 1

A 63-year-old man presented with an enlarging, darkening macule on his left posterior scalp. Biopsy revealed lentigo maligna melanoma, invasive to 2.9 mm with 2 mitoses/mm^2, without ulceration (T3a). Six months after wide local excision and negative sentinel lymph node biopsy, he developed multiple scalp lesions adjacent to his melanoma excision site which were consistent with ITMs. Given the presence of multiple lesions, he received high-dose rate brachytherapy (5 fractions of 6 Gray over 3 weeks) with moderate improvement (Fig 1). He then received topical imiquimod to the residual lesions, 5 days a week for 12 weeks, with complete clinical resolution (Fig 2, *A*). During treatment, increased erythema in areas of brachytherapy suggestive of a radiation recall effect was noted (Fig 2, *B*). He later developed pulmonary and liver metastases, for which he completed treatment with 4 doses of ipilimumab leading to a complete response. He has been disease-free for 8 years.

Case 2

A 60-year-old man presented with a "red circle" on his scalp. Biopsy demonstrated invasive malignant melanoma, Breslow thickness 1.35 mm, without ulceration (stage IB). Four months after wide local excision and sentinel lymph node biopsy, which revealed clear margins and no lymph node involvement, he developed 2 lesions surrounding the excision site consistent with satellite metastases. Given bilateral scalp metastases, high-dose rate brachytherapy was initiated (5 fractions of 6 Gray over 2 weeks) after wide local excision of the 2 metastases and negative sentinel lymph node biopsy, followed by adjuvant topical imiquimod twice daily to the entire scalp. Three months later, the patient presented with extensive forehead erythema (Fig 2, *C*), prompting discontinuation of imiquimod to all areas except the right scalp, which had not yet developed erythema. He achieved complete response after 3 months of topical imiquimod (Fig 2, *D*), with subsequent biopsies confirming no residual melanoma. One year later, screening Positron Emission Tomography/Computed Tomography revealed a lung nodule consistent with metastatic melanoma. He received 5 doses of nivolumab with radiographic resolution of pulmonary nodules and no additional metastatic disease.

Case 3

A 79-year-old man presented with a tender pink scalp nodule. Biopsy showed melanoma invasive to 3 mm thickness by Breslow, with 7 mitoses/mm^2, without ulceration. He underwent wide local excision with rotational flap reconstruction and sentinel lymph node biopsy. The excision revealed residual melanoma 1.4 mm from the nearest margin and 4.2 mm from the deep margin. The sentinel lymph node biopsy revealed no involvement with melanoma. Two months later, he developed scalp lesions which were biopsied and demonstrated metastatic melanoma (Fig 2, *E*). Given the presence of numerous ITMs on a reconstructed area, he underwent high-dose rate brachytherapy (5 fractions of 6 Gray over 2 weeks) (Fig 2, *F*), followed by 3 months of daily imiquimod application with excellent response. He has been disease-free for 7 years.

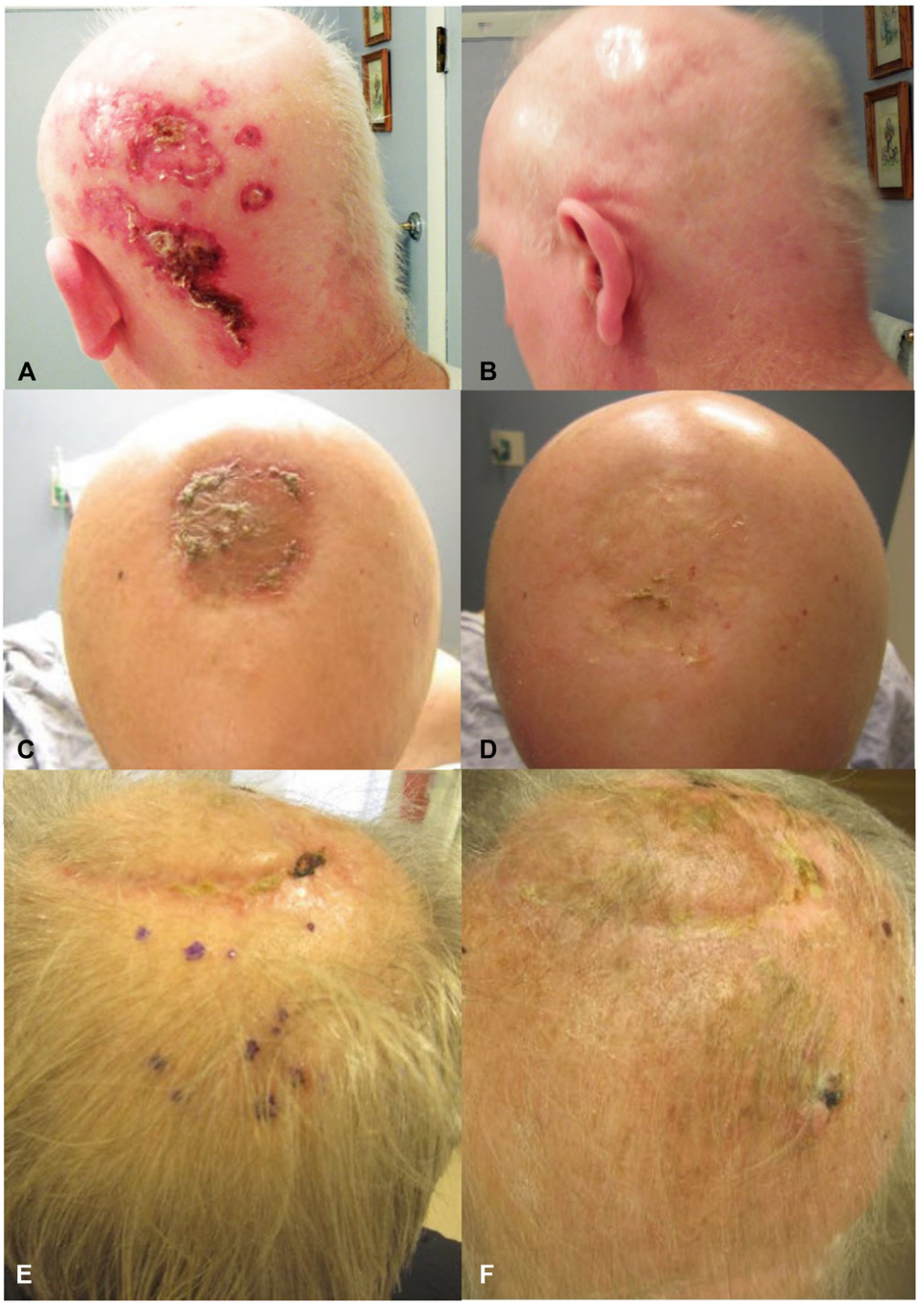

Fig 2. Metastatic melanoma regression after brachytherapy and imiquimod. **A,** Case 1: Scalp lesions at end of imiquimod with increased erythema. **B,** Case 1: Scalp lesions 2 months postimiquimod. **C,** Case 2: Scalp lesions 1 month postimiquimod. **D,** Case 2: Scalp lesions 4 months postimiquimod. **E,** Case 3: Multiple nodules surrounding excision. **F,** Case 3: Crusting nodules postbrachytherapy and preimiquimod.

DISCUSSION

Scalp melanoma may represent a more aggressive subtype with high rates of ITMs.[1,2] The standard treatment for isolated ITMs is surgical excision; however, there is currently no standard of care for multiple and diffuse ITMs that preclude surgery. A systematic review of ITM treatments showed that surgery was associated with rates of local progression between 25% and 72% at 10 to 160 months, while topical imiquimod was associated with rates of local progression between 18% and 70% over 12 to 30 months.[4]

The 3 patients treated with brachytherapy followed by topical imiquimod described here achieved rapid clearance of ITMs with minimal cutaneous adverse effects and sustained clinical remission during follow-up of at least 5 years, and for some of these patients up to 8 years. Brachytherapy allows precise targeting of skin lesions, minimizing excessive brain irradiation,[13] which is especially beneficial for patients with cutaneous metastases on complex surfaces such as the scalp. Moreover, brachytherapy may have utility for close-margin excisions, as demonstrated by case 3 who has remained disease-free. Finally, this treatment combination is well-tolerated with minimal adverse effects limited to pruritus, low-grade dermatitis, and likely permanent hair loss in the high-dose radiation area.

These 3 patients sustained clearance of cutaneous melanoma for a median follow-up of 5 years. While 2 of the patients developed distant metastases on interval screening, their metastatic disease responded well to systemic immunotherapy. It is possible that local imiquimod augmented the antitumor activity of skin-resident T cells, potentiating the response to systemic immunotherapy.[14] Since brachytherapy followed by topical imiquimod was not sufficient to prevent distant metastases in these patients, there may be differences in T cell populations that monitor the skin compared to systemic organs. This raises the question of what mechanisms are involved in generating different subsets of memory T cells in the skin compared to other organ systems. Patients with cutaneous metastases from melanoma have longer overall survival rates compared to those with distant metastases,[10] therefore, ITMs may be more responsive to treatment than distant metastases. Nonetheless, the combination of brachytherapy and topical imiquimod described here is an effective and well-tolerated treatment for ITMs.

To our knowledge, this is the first case series of unresectable cutaneous melanoma metastases on the scalp locally controlled with brachytherapy and topical imiquimod. Although, further investigations using larger patient cohorts are needed to determine the reproducibility of our findings, this combination for cutaneous melanoma metastases is a promising treatment strategy that should be considered.

We thank these 3 patients for contributing to increased knowledge of novel combination therapies for unresectable cutaneous melanoma metastases.

Conflicts of interest

None disclosed.

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