

In Situ Photoimmunotherapy

A Surgery- and Limb-Sparing Approach to the Treatment of Cutaneous Metastases in Advanced Melanoma

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

Regional cutaneous metastases of melanoma can be removed by surgical excision. However, there are limited options for treatment of these local or distant metastases when surgical removal is not feasible.

REPORT OF A CASE

When a 62-year-old white man with diabetes visited his podiatrist for routine foot care, spontaneous bleeding was noted from the intertriginous space between the left first and second metatarsals. Punch biopsy specimens revealed melanoma. Transmetatarsal amputation of the first toe was performed, and final pathologic analysis confirmed acral lentiginous melanoma of Breslow depth 2.5 mm without ulceration. Inguinal sentinel lymph node sampling detected 1 of 2 positive nodes; subsequent lymph node harvesting and analysis of 7 nodes revealed no microscopic disease. The patient received adjuvant interferon therapy for 3 months but did not tolerate the treatment. He was then followed up with observation alone.

Two years after the initial diagnosis and treatment, the patient developed numerous flesh-colored papules on the left leg. Biopsy findings were consistent with in-transit metastases of melanoma. The lesions were surgically excised, but he continued to develop similar lesions on the left leg over the next several years, requiring numerous resections and reconstructions (including more than 20 surgical procedures). Imaging studies and clinical examination did not reveal any lesions suggestive of metastatic melanoma elsewhere on the body or in the visceral organs.

THERAPEUTIC CHALLENGE

It was explained to the patient that amputation of the affected leg might reduce the risk of visceral metastases,

thereby prolonging survival. However, the patient refused this intervention.

SOLUTION

Because the patient refused leg amputation and continued to develop new in-transit cutaneous melanoma metastases, he was referred for consideration of experimental treatment with in situ photoimmunotherapy (ISPI). The goal was to spare the limb by using ISPI stimulation to prevent tumor development and further metastases. The study protocol was approved by the Northwestern University institutional review board prior to study initiation.

Cutaneous melanoma metastases with individual tumor diameters greater than 1 cm were selected for ISPI therapy, and treatment was limited to a 20 × 20-cm total area of tumor. Immunomodulation was first achieved by twice-daily application of imiquimod, 5%, cream to 2 selected tumor treatment sites kept under plastic film occlusion for 24 hours using transparent dressing. After 2 weeks of occluded topical imiquimod treatment, the patient received an injection of lidocaine, 1%, with 1:200 000 epinephrine and 1:10 sodium bicarbonate, 8.4%, followed by 10 mL of an intralosomal photosensitizing dye (indocyanine green [ICG], 0.25%) into the targeted cutaneous metastases. Each targeted tumor lesion was then irradiated for 10 minutes with a continuous-wave, 810-nm diode laser at a fluence of 1 J/cm². This entire 2-week regimen was immediately repeated once, and then the second course was immediately followed by a 2-week course of occluded topical imiquimod only. A lesional biopsy of each targeted lesion was performed 5 weeks after completion of the final imiquimod treatment to assess the presence or absence of residual melanoma. Neighboring lesions not targeted with ISPI treatment were also followed up to assess for resolution of tumor.

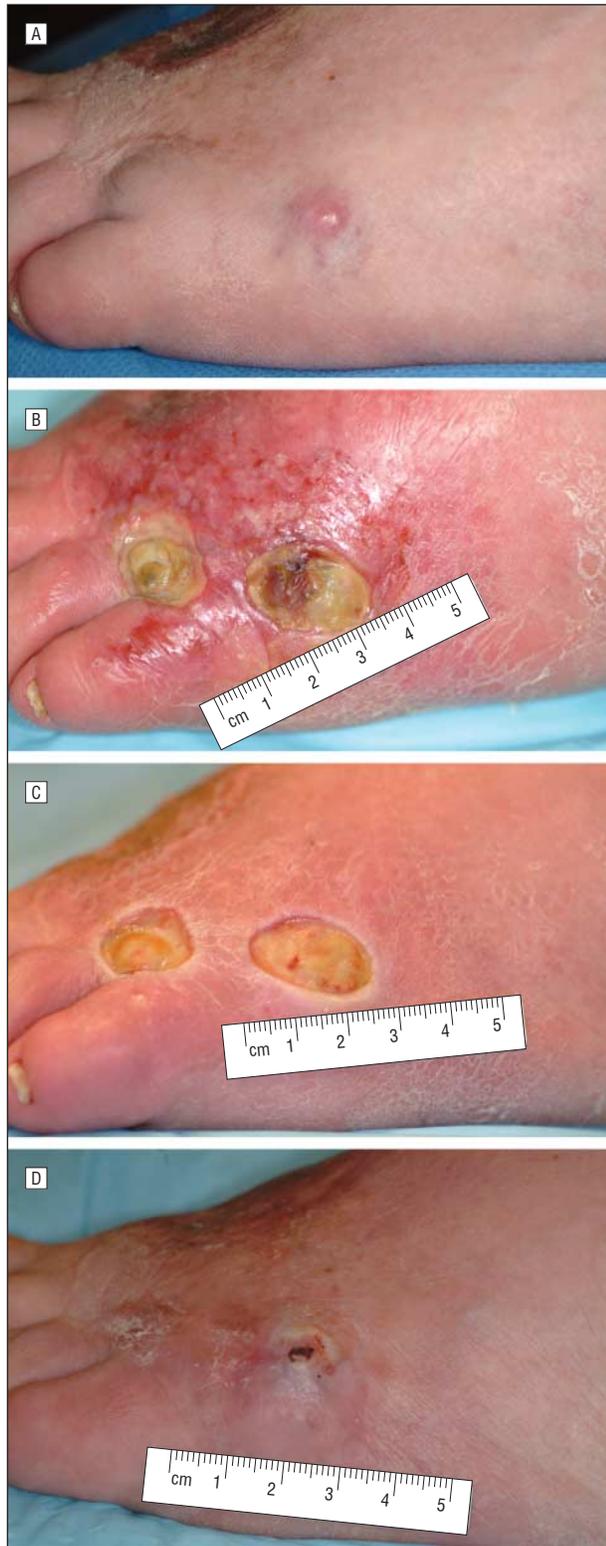


Figure 1. Clinical images of the patient. A, Before treatment, the patient had multiple tumor nodules of the left foot. B, After 6 weeks of twice-daily imiquimod treatment and 2 phototherapy treatments, the tumors were ulcerated. C, At week 8, there was evidence of granulation tissue. D, Five months after initiation of cycle 1, the distal lesion had resolved, while the lateral lesion showed evidence of residual melanoma. A second cycle of treatment was initiated.

When therapy commenced in the patient, 2 subcutaneous nodules on the dorsal aspect of the left foot were treated (**Figure 1**), and 2 nearby tumors not targeted

by ISPI therapy were clinically followed up. Biopsy specimens taken 5 weeks after completion of topical imiquimod treatment showed superficial scarring and repair changes in the 2 target lesions. One nontargeted neighboring tumor showed clinical resolution, while another nontargeted lesion did not. One month after completion of the first cycle of treatment, the patient developed a recurrent subcutaneous nodule in one of the sites treated with ISPI. A wedge biopsy specimen demonstrated recurrent metastatic melanoma. The patient then entered a second entire cycle of therapy that targeted this recurrent subcutaneous nodule on the foot. After this cycle, the targeted lesion resolved clinically. Beginning 5 weeks later, additional metastatic melanoma nodules appeared, and a third cycle of therapy was eventually commenced (3 months after initiating the second cycle).

In the 1 year prior to ISPI treatment, the patient experienced 12 recurrences or new metastatic nodules, but after beginning ISPI, he experienced only 3 such recurrences or new nodules. Given that the overall recurrence rate of new cutaneous tumors appeared to have slowed, the patient continued indefinitely to receive recurrent cycles of ISPI when new or recurrent nodules occurred, in support of the initial goal of limb sparing.

Imaging studies did not detect spread of metastatic melanoma beyond the left lower leg. Computed tomography of the chest, abdomen, and pelvis 10 months after initiation of ISPI therapy showed no areas suggestive of metastasis, and at 18 months after initiation of ISPI, he remained free from detectable visceral metastases.

Overall, the patient's ISPI treatments were well tolerated with no serious adverse events. Concurrent minor adverse events included local pain and local wound ulceration that resolved with wound care.

COMMENT

This case demonstrates the potential utility of ISPI treatment for patients who have metastatic melanoma with cutaneous metastases. In several instances, clinical remission of cutaneous metastases was achieved; this remission was sometimes combined with temporary histologic resolution of the target lesions (**Table**). More importantly for the patient, he reduced his risk of distant metastases without limb amputation. One prior report¹ showed complete remission of both cutaneous and visceral metastases for up to 20 months in 2 subjects with advanced metastatic melanoma and cutaneous metastases treated with ISPI. However, this research did not specifically address the challenge of limb sparing in the context of metastatic disease.

In situ photoimmunotherapy, a form of combination laser immunotherapy and toll-like receptor (TLR) agonist stimulation, is a tumor-directed immunotherapy technique in which an intense local immune response is triggered within and around a preexisting deposit of tumor such as a metastasis.²⁻⁴ In ISPI, the therapeutic intervention commences with pretreatment using a TLR agonist, in this case topical imiquimod, which has been reported to have action against lentigo maligna⁵⁻⁸ and invasive melanoma.^{1,9-11} Subsequent to this topical therapy, ISPI pro-

Table. Clinical and Histologic Outcomes of Target and Nontarget Lesions Monitored in ISPI Cycles 1 and 2

Lesion	Site	Clinical Resolution After Cycle 1?	Histologic Resolution After Cycle 1?	Clinical Resolution After Cycle 2?	Histologic Resolution After Cycle 2?
1	Foot, left, mid-5th metatarsal	Yes	Yes ^a	No	No
2	Foot, left, between 4th and 5th metatarsal	Yes	Yes	NA	NA
3	Foot, left, proximal phalanx of 4th toe	No	Biopsy not performed	No	Biopsy not performed
4	Foot, left, proximal phalanx of 5th toe	Yes	Biopsy not performed	NA	NA

Abbreviations: ISPI, in situ photoimmunotherapy; NA, not applicable.

^aHowever, a recurrent nodule to this area was noted 1 month later.

ceeds via a selective photothermal interaction achieved in the tumor by application of laser energy over a laser-absorbing dye such as ICG. The laser and ICG collectively provide a further means for local destruction of tumor cells in situ. Tumor cells killed by this method then serve as an antigenic source for a local immune response that is further stimulated by the postlaser use of additional immunoadjuvants (eg, imiquimod). The infrared laser technique used in ISPI was developed in animal models, and its combination with immunoadjuvants has been shown to cure some solid tumors with and without metastases.¹²⁻¹⁸ It is important to distinguish this unique form of immunotherapy from palliative techniques that simply ablate tumor in that ISPI may invoke a systemic response and therefore have indirect action in destroying tumors not specifically targeted by the therapy.

In situ photoimmunotherapy is a promising technique for treating metastatic melanoma with cutaneous metastases, a condition for which, to our knowledge, there is no consistently effective therapy. Therapies that have been tried include excision, carbon dioxide laser ablation, radiation therapy, intralesional therapy, hyperthermic isolated limb perfusion, isolated limb infusion, and systemic chemotherapy.¹⁹ However, cumulative 5-year patient survival with conventional therapies is low, around 18%, hence justifying the exploration of the potential utility of therapeutic approaches such as ISPI.²⁰

Undoubtedly, the most important outcome measure in this study is the survival of the patient, who continues with a good quality of life 18 months after initiating ISPI treatment. After enrollment into the study, the patient developed local metastatic nodules at a rate one-sixth that of the rate prior to therapy initiation. The suggested possibility of a systemic effect of the treatment is based on this reduction of metastases as well as the clinical resolution of at least 1 nontargeted neighboring tumor nodule. Also of importance, limb function and ability to walk were preserved. Maintenance of mobility, independence, and quality of life during what may be end-of-life treatment obviously is of great importance to patients living with advanced melanoma. Relative to the costs of surgical excision or the use of systemic or chemotherapeutic agents, this approach may also be more cost-effective.

These preliminary data suggest that the benefit detected in this patient may be achievable in selected other patients. To better understand the utility of ISPI therapy in the context of melanoma metastatic to skin, we have since offered this therapy under protocol to additional patients with melanoma. Larger studies with representative cohorts may clarify the extent to which these find-

ings are generalizable. Until then, given the toxic effects of other available therapies, ISPI may be a potentially useful tissue-sparing and function-preserving treatment in melanoma patients with cutaneous metastases.

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Submissions

Clinicians, residents, and fellows are invited to submit cases of challenges in management and therapeutics to this section. Cases should follow the established pattern. Manuscripts should be prepared double-spaced with right margins nonjustified. Pages should be numbered consecutively with the title page separated from the text (see Instructions for Authors [<http://archderm.ama-assn.org/misc/fora.dtl>] for information about preparation of the title page). Clinical photographs, photomicrographs, and illustrations must be sharply focused and submitted as separate JPG files with each file numbered with the figure number. Material must be accompanied by the required copyright transfer statement (see authorship form [http://archderm.ama-assn.org/misc/auinst_crit.pdf]). Preliminary inquiries regarding submissions for this feature may be submitted to Erik J. Stratman, MD (stratman.erik@marshfieldclinic.org). Manuscripts should be submitted via our online manuscript submission and review system (<http://manuscripts.archdermatol.com>).