CASE REPORTS
SPECIAL TOPIC
Journal of Drugs in Dermatology

Regression of Internal Melanoma Metastases Following Application of Topical Imiquimod to Overlying Skin

Anne K. Miller BS, Reginald Dusing MD, Aaron Meggison MD, Daniel Aires MD
University of Kansas School of Medicine, Departments of Dermatology and Radiology, Kansas City, KS

ABSTRACT

The prognosis for metastatic melanoma is grim, and treatment options are limited. Imiquimod is a topically applied immune-modulator that has been used to treat superficial cutaneous melanoma, but has not been reported to treat metastatic melanoma. We report a patient whose liver and iliac fossa melanoma metastases regressed after topical application of imiquimod cream to overlying skin. This supports further investigation of the potential use of imiquimod for metastatic melanoma.

J Drugs Dermatol. 2011;10(3):302-305.

INTRODUCTION

Imiquimod was approved by the U.S. Food and Drug Administration (FDA) in 1997. The 5% formulation is known under the trade names of Aldara and Beselna. A 3.75% formulation is now available under the trade name Zyclara. Aldara and Zyclara are manufactured by Graceway Pharmaceuticals; Beselna is manufactured by Mochida. Imiquimod binds cell surface toll-like receptors 7 and 8, and induces immune responses. Cells activated by imiquimod secrete cytokines including interferon-alpha, tumor necrosis factor-alpha and interleukins 6 and 12.[1] These cytokines activate Langerhans cells and initiate both innate and acquired immune responses.[2–3] Imiquimod cream is widely used to treat actinic keratoses, superficial basal cell carcinomas, warts and superficial melanomas.[4] It is applied topically to the skin 2–5 times per week, depending on the type of lesion and the patient's response. Duration of imiquimod treatment typically ranges from 6–16 weeks.[4] We report on a case of apparent regression of metastatic melanoma with the use of superficial imiquimod.

CASE REPORT

A 55-year-old male with a history of coronary artery disease and hyperlipidemia presented with an upper gastrointestinal bleed, melena and anemia requiring transfusion. In March 2008, an EGD showed a gastric mass originally thought to be poorly differentiated adenocarcinoma; this was treated with a gastrectomy one month later. Surgical pathology results showed gastric melanoma. A primary 0.16 mm melanoma was subsequently found on the patient's right arm, and treated with wide local excision. PET and CT scans in May 2008 showed a metastatic mass in the right iliac fossa adjacent to the iliacus muscle. At this point, a watchful waiting approach with no systemic chemotherapy was adopted.

The patient had been prescribed imiquimod cream to treat a basal cell carcinoma on the left lower eyelid. On his own, the patient decided in June 2008 to start applying imiquimod cream three times per week to his abdominal skin overlying the melanoma metastasis in his lower right quadrant. A second PET scan in August 2008 showed increased uptake in the right iliac fossa lesion as well as new metastatic lesions in the liver and right supraclavicular area. Due to disease progression, the decision was made to pursue a course of IL-2. He stopped the imiquimod to prepare for this, after having used it for three months. The patient was admitted for 14 doses of IL-2 in September 2008. After dose 13 the patient developed IL-2 associated myocarditis, so treatment was discontinued. CT scan in October 2008 showed slight increases in the hepatic metastases and no growth of the iliac fossa metastasis (Figures 1 and 2). It was determined the patient could not tolerate another cycle of IL-2. Both the patient and the oncologists agreed to take a watchful waiting approach because the patient was asymptomatic at that time.

> After August 2009 he continued imiquimod as monotherapy to a larger area, including both the anterior pelvis and the right upper quadrant. Surprisingly, his metastatic lesions regressed, and one completely disappeared. It is possible that application of imiquimod to a larger area could have had an effect on the metastatic lesions.

In October 2008 the patient restarted topical imiquimod, this time to his entire right abdomen. PET and CT scans in January 2009 showed partial resolution of the previously metabolically active foci in the liver, and a decrease in size of the right iliac fossa metastasis. At the time of his January 2009 scans, the patient had been applying the imiquimod cream for approximately six months: three months before his IL-2 treatment, and three months afterward. Encouraged by the January 2009 scans, he continued to apply topical imiquimod cream to his abdomen and pelvis three times per week. Scans from September 2009 showed complete resolution of his hepatic lesions and a continued decrease in the size of the right iliac fossa metastasis.

The patient's most recent CT scans from December 2009 showed no evidence of a hepatic mass and no continued growth of the iliac fossa mass (Figures 3 and 4). Visual examination of the patient's abdomen and pelvic region in March 2010 showed multiple red pustules approximately 8 mm in diameter concentrated in the two regions he had been applying the imiquimod cream (Figure 5). This was the only adverse effect of the imiquimod treatment according to the patient.

DISCUSSION

Melanoma is a very aggressive and often fatal skin cancer, and its incidence is rising worldwide. In the United States, the incidence rate is 10–25 per 100,000.[5] Risk factors for the development of melanoma include having a large number of nevi (especially dysplastic nevi), UV radiation and sun exposure, immunosuppression, previous occurrence of melanoma and having a family history of melanoma.[7–8] The five-year survival rate for patients with distant metastases is only 10 percent with a median survival of six to 12 months.[6]

Spontaneous regression of melanoma metastases is extremely rare. Spontaneous regression is defined as a complete or partial disappearance of a metastatic lesion in the absence of therapy —or in the presence of therapy that is considered inadequate to yield significant tumor response. The incidence of spontaneous regression of malignant melanoma is approximately one in 400 patients presenting with metastatic disease.[9]

This report describes a patient with stage IV melanoma, with metastases to the stomach, liver, and iliac fossa. For patients with stage IV melanoma, systemic chemotherapy is indicated, despite its limited success.[10] The choices for single-agent chemotherapy include cytotoxic agents and cytokines.[11] The above patient received a single round of IL-2 monotherapy, which has a response rate of 16–21.6 percent.[6] Due to this patient's development of interleukin-induced myocarditis and the slow progression of his lesions on multiple PET and CT scans, it was decided that he would not undergo any more chemotherapy at that time. On his own, the patient had started applying topical imiquimod three times per week to a small area of abdominal

FIGURE 1. CT scan from October 2008 after IL-2 treatment showing a hepatic metastasis that had grown slightly after IL-2 therapy. Measurements of lines 1 and 2 are 12.8 and 22.1 mm, respectively.

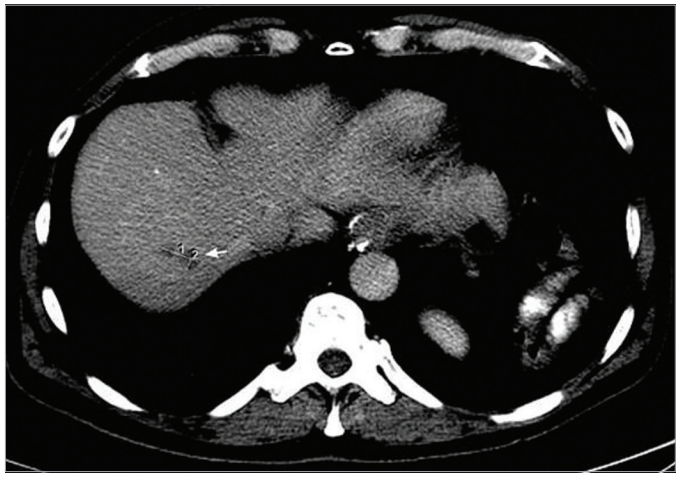


FIGURE 2. CT scan from October 2008 after IL-2 treatment showing a stable iliac fossa metastasis. Measurements of lines 1 and 2 are 12.8 and 15.3 mm, respectively.

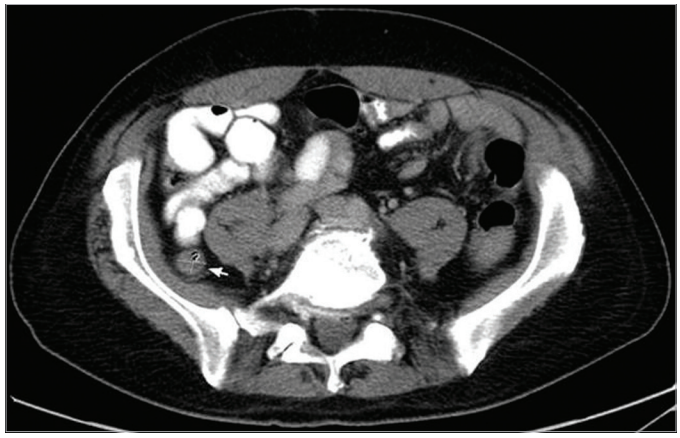


FIGURE 3. CT scan from December 2009 after large-area imiquimod showing no evidence of a hepatic mass.

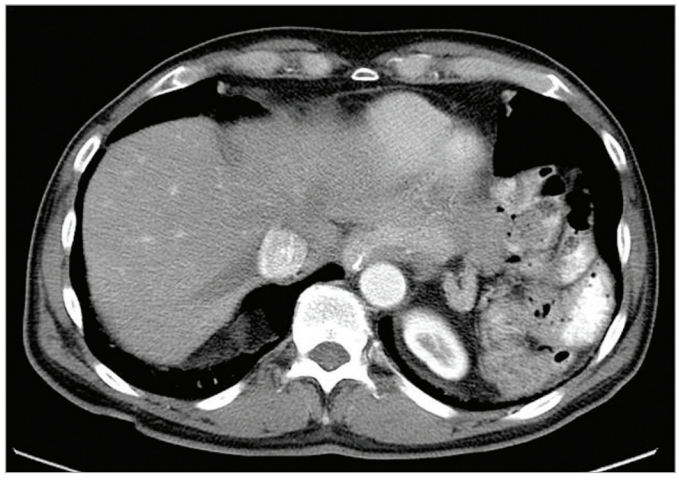


FIGURE 4. CT scan from December 2009 after large-area imiquimod showing a decrease in size of the iliac fossa metastasis compared to scans after IL-2 treatment. Measurements of lines 1 and 2 are 8.5 and 6.3 mm, respectively.

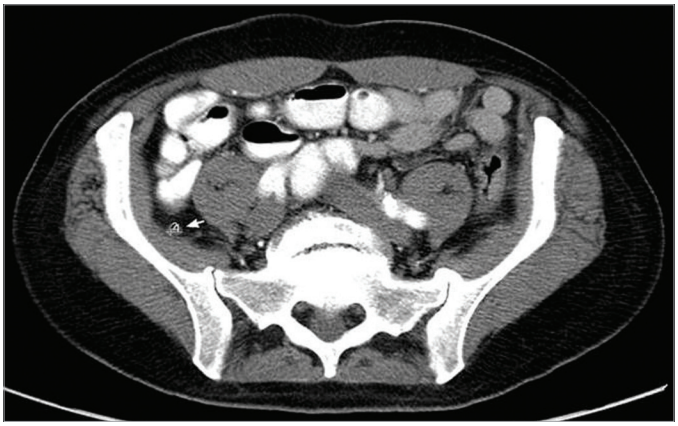
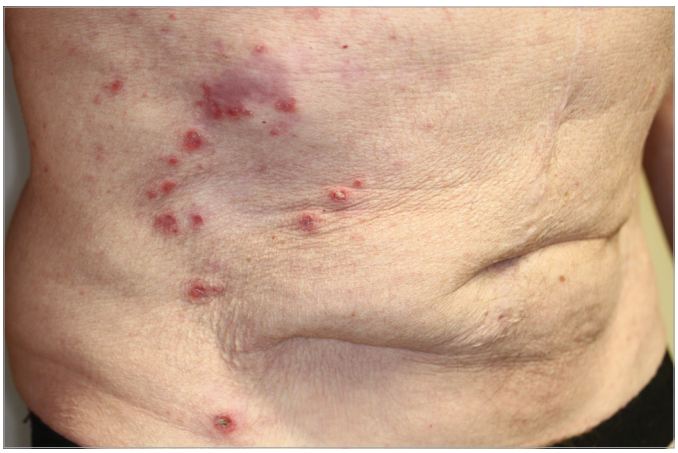


FIGURE 5. Photo from June 2010 of patient's abdomen after 20 months of applying imiquimod to a large area of his right upper and lower quadrants three times a week.



skin overlying the metastatic lesions. After August 2009 he continued imiquimod as monotherapy to a larger area, including both the anterior pelvis and the right upper quadrant. Surprisingly, his metastatic lesions regressed, and one completely disappeared. It is possible that application of imiquimod to a larger area could have had an effect on the metastatic lesions.

Although the cure rate after only one treatment of IL-2 chemotherapy is very low, it could nonetheless have been the reason for this patient's tumor regression. However, based on the timing of his lesional growth and regression, we believe it is more likely that the imiquimod was responsible for regression of his lesions.

While use of imiquimod for internal melanoma metastases has not been reported, there is evidence that imiquimod is effective for off-label treatment of cutaneous melanoma. A patient presenting with multiple cutaneous and subcutaneous metastases on the scalp showed complete regression of lesions after 17 months of topical imiquimod therapy.[12] Another study looked at seven patients with lentigo melanoma treated with topical imiquimod for 12 weeks; at 19 months follow-up, six of the seven patients showed both clinical and histologic resolution.[13] Of note, imiquimod is approved for treatment of actinic keratoses, superficial basal cell carcinomas, and external genital warts. Actinic keratoses are treated twice a day for no more than 16 weeks, superficial basal cell carcinomas are treated five times a week for six weeks, and genital warts are treated three times a week for no more than 16 weeks. The cream is to be applied in a thin layer and left on for eight hours before washing it off.[14] Use of imiquimod in cutaneous melanoma is off-label and not supported by the manufacturers. The patient we report followed an alternating two week application schedule that used significantly more than the amount recommended for superficial basal cell carcinoma. He used two full packets, one on the abdomen and one on the pelvis, three times per week, for a total of six packets in the first week. This typically caused sufficient discomfort that he would use half of a packet on each area three times per week, for a total of three packets in the second week. He used this alternating schedule for nearly the entire treatment course, and continues to do so.

In contrast to the multiple common and potentially serious side effects of systemic chemotherapy, the only common adverse effect of topical imiquimod is skin breakdown at the application site.[3] This patient experienced some skin breakdown, but persisted with treatment. Although imiquimod has only been indicated for the use of cutaneous diseases, this report supports further exploration of the potential for topical imiquimod or other topical therapies to play a role in treating systemic disease. This may be useful for those who cannot tolerate chemotherapy.

DISCLOSURES

None of the authors have any relevant conflicts of interest, financial or otherwise.

REFERENCES

1. Lacarrubba F, et al. Advances in the use of topical imiquimod to treat dermatologic disorders. *The Clin Risk Manag*. 2008;4:87-97.
2. Miller RL, et al. Imiquimod applied topically: A novel immune response modifier and a new class of drug. *Int J Immunopharmacol*. 1999;21(1):1-14.
3. Sauder DN. Imiquimod: Modes of action. *British Journal of Dermatology*. 2003;149(Suppl 66):5-8.
4. American Society of Health-System Pharmacists. Imiquimod Topical. AHFS Consumer Medication Information. 2009.
5. Atkins MB, Lotze MT, Dutcher JP, et al. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: Analysis of 270 patients treated between 1985 and 1993, *J Clin Oncol*. 1999;17:2105–2116.

6. Balch C, Buzaid A, Soong S, et al. Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. *J Clin Oncol*. 2001;19(16):3635–3648.
7. SkinCancerNet. Who is most at risk for melanoma. Available at: http://www.skincarephysicians.com/skincancernet/who_is_most.html. Accessed December 21, 2009.
8. Greene MH. The genetics of hereditary melanoma and nevi. 1998 Update. *Cancer*. 1999;86(11):2464–2477.
9. Kalialis LV, Drzewiecki KT, Mohammadi M, et al. Spontaneous regression of metastases from malignant melanoma: Case report. *Melanoma Res*. 2008;18(4):279-283.
10. Bajetta E, Del Vecchio M, Bernard-Marty C, et al. Metastatic melanoma: Chemotherapy. *Semin Oncol*. 2009;29(5):427-445.
11. Garbe C, Peris K, Hauschild A, et al. Diagnosis and treatment of melanoma: European consensus-based interdisciplinary guideline. *Eur J Cancer*. 2010;46(2):270-283.
12. Heber G, Helbil D, Ponitzsch I, et al. Complete remission of cutaneous or subcutaneous melanoma metastases of the scalp with imiquimod therapy. *J Dtsch Dermatol Ges*. 2009;7(6):534-536.
13. Mahoney MH, Joseph MG, Temple C. Topical imiquimod therapy for lentigo melanoma. Ann Plast Surg. 2008;61(4):419-424.
14. Aldara: Package insert. Bristol, NJ: Graceway Pharmaceuticals; 2009.

ADDRESS FOR CORRESPONDENCE

Anne K. Miller, BS
3838 Rainbow Blvd, Apt 1402
Kansas City, KS 66103
Phone 316-253-9928
E-mail..... amiller@kumc.edu