

Topical treatment of cutaneous metastases of malignant melanoma using combined imiquimod and 5-fluorouracil

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Received: 23 May 2011 / Accepted: 1 July 2011
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Summary *Background* Despite multiple available options, the treatment of cutaneous melanoma metastases is often unsuccessful. Based on the hypothesis that imiquimod and 5-fluorouracil have synergistic antitumor properties, we used this topical combination to treat several patients. *Aim* Our objective was to investigate the treatment combination in a small cohort of patients with surgically non-resectable melanoma metastases. *Methods* The lesions of 5 patients with multiple cutaneous metastases were treated topically, 5 days per week, with 5-fluorouracil in the morning and imiquimod at night. *Results* 45 lesions were treated. A clinical response was seen in 44 lesions, with a complete response in 19 lesions and a partial response in 25. Stable disease was confirmed in the 1 remaining lesion. No patients developed new lesions during treatment. However, one patient had a recurrence 6 months after treatment discontinuation, followed by a partial response when rechallenged. *Conclusions* The imiquimod and 5-fluorouracil combination is effective. That patients did not develop new, distant lesions suggests the achievement of locoregional control, probably by the induction of antitumor immune response.

Keywords Imiquimod · 5-fluorouracil · Melanoma · Skin metastases · Tumor immunology

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Introduction

Skin metastases of malignant melanoma can be difficult to treat. Surgery is the first line of treatment in patients whose disease is limited. For patients with more extensive disease restricted to one limb, isolated limb perfusion can be proposed. Some investigators have explored the idea of using intralesional agents such as bacille Calmette-Guerin (BCG) [1] or interleukin 2 (IL-2) [2] in order to stimulate immune response. A recent report by Hodi *et al.* showing that ipilimumab improves overall survival in patients with metastatic disease [3] has confirmed the potential of immunotherapy in the treatment of metastatic melanoma.

In the last decade, immunotherapy efforts have focused on imiquimod, a synthetic immunomodulatory molecule. Imiquimod is licensed for the treatment of anogenital warts, actinic keratosis and superficial basal cell carcinoma. Imiquimod has also been found to be useful for the treatment of nodular basal cell carcinoma, superficial squamous cell carcinoma [4] and lentigo maligna [5]. It was first used to treat cutaneous metastatic melanoma in 2000 [6–9]; previously, 5-fluorouracil cream, which is licensed for the treatment of Bowen's disease and actinic keratosis, had been used [10].

More recently, Ondo *et al.* reported the efficacy of a topical combination therapy using 5-fluorouracil and imiquimod creams for cutaneous squamous cell carcinoma in situ in patients whose disease failed to respond to topical monotherapy [11]. Given these convincing therapeutic results, we decided to validate the case report effectiveness of imiquimod and 5-fluorouracil creams to treat cutaneous metastases of malignant melanoma in a series of patients.

Table 1 Patients' characteristics

Patient	Age (years)	Sex	Main antecedents	Site of lesion	Type of lesion	Number of lesions	C	SC	Previous treatment
1	88	F	atrial fibrillation	leg	mixed	17	2	15	radiotherapy
2	72	F	cardio-vascular risk factor	leg	cutaneous	5	5	0	surgery
3	79	F	cardio-vascular risk factor	leg	cutaneous	7	7	0	surgery
4	84	F	acute myocardial infarction	leg	cutaneous	3	3	0	surgery
5	82	F	end-stage heart failure	leg	cutaneous	13	13	0	none

F: female; C: cutaneous; SC: subcutaneous

Methods

Five patients diagnosed with stage III melanoma according to the American Joint Committee on Cancer guidelines were recruited between October 2007 and July 2010. Each patient had one or more cutaneous and/or subcutaneous melanoma metastases, and had reached a point where further conventional therapies were no longer appropriate. All patients showed histological evidence of a primary melanoma, with subsequent, histologically proven metastatic deposits. Systemic evaluation revealed no evidence of internal metastases after whole body scanning. None of the patients had received either previous or concomitant chemotherapy, or interferon- α . Clinical evaluation was performed every 3 months.

From their initial appointment, patients were prescribed a daily application, 5 days per week, of 5-fluorouracil cream (Efudix[®]) in the morning and 5% imiquimod cream (Aldara[®]) at night. These were applied topically to each lesion, including a 1-cm area around the lesion, and covered with an occlusive dressing. This regimen was continued until a response was seen. If any area became painful, patients could suspend treatment until the skin had healed. If a lesion disappeared, becoming invisible and impalpable, treatment of the lesion was stopped. If a partial response was observed, treatment was maintained.

Results

Five patients were recruited to the study. All were women ranging from 72 to 88 years of age (average age: 81). One of the patients exhibited a mixture of cutaneous and subcutaneous lesions, while the others had purely cutaneous disease. The patients' characteristics are shown in Table 1.

In total, 45 lesions were treated, 30 cutaneous and 15 subcutaneous. The combined results show that a clinical response was seen in 44 lesions (98%), with a complete response in 19 lesions (42%) (Fig. 1, Fig. 2) and a partial response in 25 (56%). In the 1 remaining lesion (2%), stable disease was confirmed. The analysis according to lesion type shows that of the 30 cutaneous lesions treated, 19 (63%) showed complete response, 10 (33%) partial response and 1 (3%) stable disease. A skin biopsy specimen was performed in patients 1 and 4, with their consent, 6 months after obtaining a complete clinical response. A complete histological clearance of the skin lesion was achieved in these 2 cases (Fig. 3). Of the 15 subcutaneous metastases, all showed partial response and none a complete response. Overall no patients in our study progressed with either new cutaneous or subcutaneous metastases, with follow-up since the treatment initiation of 3, 21, 21, 30 and 33 months. The results are summarized in Tables 2 and 3.

Table 2 Response to treatment

Patient	Treatment duration (months)	Number of lesions	Cutaneous lesions			Subcutaneous lesions			Number of ulcerated lesions
			CR	PR	SD	CR	PR	SD	
1	21	17	2				15	2 ^a	
2	24	5	2	3				2	
3	21	7	4	2	1			5	
4	27	3	3					3	
5	3	13	8	5				12	

CR: complete response; PR: partial response; SD: stable disease

^a cutaneous lesions

Table 3 Summary of results

	Number of lesions	Complete response	Partial response	Stable disease	Progressive disease
All lesions	45	19 (42%)	25 (56%)	1 (2%)	0
Subcutaneous lesions	15	0	15 (100%)	0	0
Cutaneous lesions	30	19 (63%)	10 (33%)	1 (3%)	0

There was considerable variation in the length of time for lesions to respond to treatment. All complete responses were observed after ulceration had developed (Fig. 4). When there was partial response, local inflammation was more modest, resulting in an erythematous reaction. In 2 patients, treatment was stopped after obtaining a complete response. One patient was confirmed to be disease free at a follow-up of 6 months. However, a second patient experienced a recurrence 6 months after stopping treatment. After rechallenge, a partial response was noted within 3 months, and no visceral metastasis appeared.

Discussion

5-Fluorouracil is an anti-metabolite able to induce apoptosis of tumor cells. Specifically, the fluorouracil-induced inhibition of DNA synthesis and lack of normal RNA results in unbalanced cell growth and subsequent cell death. Its effects are enhanced in the presence of some cytokines, including INF- α , - β , - γ and IL-12 [12].

Imiquimod, an imidazoquinoline amine, stimulates immune response, particularly by binding to the toll-like receptor 7 of monocytes and macrophages. This binding induces a dose-dependent synthesis of mRNA of various cytokines (INF- α , - γ , IL-1, -6, -8, -12) involved in the activation of effector cells and lymphocyte response of the Th1 profile [13, 14]. Imiquimod has also been found to induce apoptosis in certain cells lines of malignant

melanoma - both in vitro and in vivo - independently from membrane-bound death receptors [15]. Some authors also suggest that imiquimod modulates angiogenesis [16].

Imiquimod and 5-fluorouracil creams therefore possess distinct antitumor properties. Apart from an additive effect associated with the induction of apoptosis in malignant cells, the increase of the action of 5-fluorouracil in the presence of INF- α , INF- γ and IL-12 suggests a possible synergistic effect.

Powell *et al.* consider a patient's ability to develop an inflammatory reaction to imiquimod as a strong predictor of therapeutic benefit in treatment of melanoma in situ [17]. In our study, all complete responses were preceded by ulceration. Twenty of the 25 partial responses followed a single erythema. The presence of an inflammatory reaction is related to the mechanism of action of imiquimod, and the intensity of the reaction appears to predict response to the molecule.

Although the regression of lesions in our patients is important, we must also emphasize the absence of new distant lesions during a mean follow-up period of 22 months since the treatment initiation. This fact could reflect the typically slow evolution of the disease in these patients. However, it could also imply that combined treatment with topical imiquimod and 5-fluorouracil may lead to locoregional control by stimulating an effective antitumor immune response. Evidence for the latter explanation is



Fig. 1 Cutaneous melanoma metastases before topical treatment



Fig. 2 Complete response after 3 months of topical combination of imiquimod and 5-fluorouracil

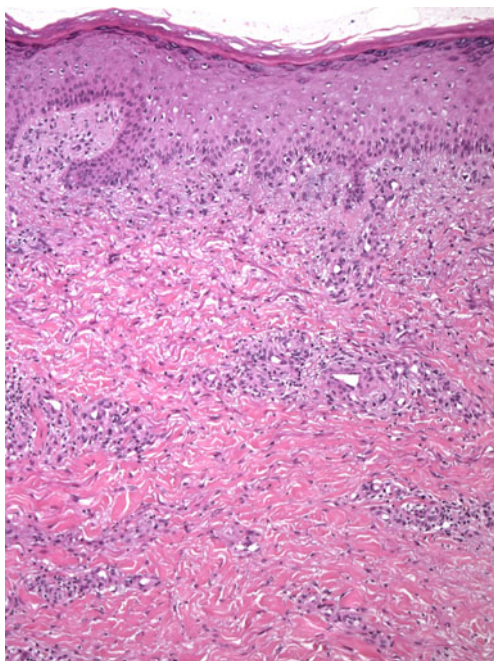


Fig. 3 No evidence of cutaneous melanoma metastasis in skin biopsy specimen obtained at 6 months after the end of the topical combination of imiquimod and 5-fluorouracil

reinforced by the cases of vitiligo induced by imiquimod. Pigmentation changes involving vitiligo-like hypopigmentation have been described in association with the topical application of imiquimod cream for genital warts [18] and basal cell carcinoma [19]. Although the etiology of vitiligo remains unclear, it appears as a cytotoxic T-lymphocyte-mediated autoimmune disease. Imiquimod could contribute to its occurrence by enhancing the Th1 response, involving cytotoxic T cell activity directed toward melanocyte surface antigens [20].

The poorer response obtained with the subcutaneous lesions is probably partly due to limited penetration of the topical preparation and perhaps different tumor biology.



Fig. 4 Example of ulceration induced by the combination of imiquimod and 5-fluorouracil after 3 months

Conclusion

We report here the first series of cutaneous melanoma metastases treated with the topical combination of imiquimod and 5-fluorouracil. Our results indicate that this seems to offer an alternative treatment for soft-tissue metastases of melanoma, particularly cutaneous lesions in patients for whom surgery may be contraindicated or when surgery could have considerable functional or cosmetic consequences. The absence of new, distant lesions suggests the achievement of locoregional control, probably due to the induction of antitumor immune response. In the near future, controlled studies are needed to prove the effectiveness of this combination as a novel and promising treatment modality.

Funding source None.

The authors declare they have no conflict of interest to declare.

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