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Review

Topical treatment of melanoma skin metastases with imiquimod: a review

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Abstract

Background: At present, case studies are the only source of results on imiquimod (IMQ) as monotherapy in cutaneous metastases from melanoma. We analyzed these studies in the literature with the aim to review the efficacy of IMQ as topical treatment for melanoma skin metastases.

Objective: The aim of our review was to critically assess the studies evaluating the monotherapy with IMQ cream in the treatment of cutaneous metastases from melanoma.

Methods: A PubMed search was conducted using the term "melanoma" combined with "metastases" and "imiquimod".

Results: 57 studies were identified of which 46 did not meet inclusion criteria, leaving 11 case studies. Overall, 17 patients were treated in these 11 studies. The main treatment choice was 5% IMQ cream applied once daily (for 6-8 hours), five days per week under occlusive conditions and this regimen was used in 8/17 patients (47.1%). IMQ was applied 3 times weekly in 4/17 patients (23.5%), daily in 2/17 patients (11.8%), and twice daily in 2/17 patients (11.8%). Treatment length was variable, with a mean duration of 22 weeks (range from 8 weeks to 72 weeks).

Conclusions: The majority of studies showed that IMQ is an effective and safe treatment for metastases of melanoma. Even if this treatment doesn't stop the disease progression, it is useful in clearing cutaneous metastases.

Keywords: topical melanoma treatment, imiquimod, melanoma

Introduction

Topical drugs are becoming standard treatments for many types of skin cancers [1, 2]. These include the use of 5-fluorouracil, imiquimod (IMQ), diclofenac, ingenol mebutate, and retinoids. They are generally reserved for the treatment of basal cell carcinoma, squamous cell carcinoma, HPV-induced genital warts, Bowen's disease, erythroplasia of Queyrat, Paget's disease, trichoepithelioma, and lentigo maligna [3, 4]. Moreover, the use of non-surgical treatments for melanoma is becoming common in patients who refuse surgery or in patients for whom surgery is not indicated.

Cutaneous and oral melanoma in situ were treated with IMQ with excellent results at follow-up and a complete response was observed in all patients in some studies [5-7]; in a small number of cases, even invasive cutaneous melanoma was treated by IMQ [8, 9]. At present, case studies are the only source of results on IMQ as monotherapy in cutaneous metastases. We analyzed these studies in the literature with the aim to review the efficacy of IMQ as topical treatment for melanoma skin metastases.

IMQ is a synthetic Toll-like receptor 7 (TLR7) agonist. It is an immune response modifier with potent antiviral and antitumor effects. IMQ targets predominantly TLR7 expressing plasmacytoid dendritic cells and Langerhans cells, with secondary recruitment and activation of other inflammatory cells. Activation of TLR7 results in the stimulation of the innate and acquired immune responses, in particular cell mediated immune pathways.

IMQ revealed multifactorial effects toward inhibition of melanoma development. It elicits an anti-invasive effect on human melanoma cells by regulating matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs). A concentration-dependent decrease in MMP-2 and MT1-MMP protein levels and a concentration-dependent increase in TIMP-1 and -2 protein levels by IMQ was observed in melanoma cell lines [10].

IMQ also strongly inhibits melanoma tumor development through prompt mobilization of plasmacytoid dendritic cells and by triggering their cytotoxic functions and upregulating type 1 IFN response genes. IMQ drastically blocks tumor vascularization by inducing the downregulation of angiogenic factors such as vascular endothelial growth factor, angiogenin, IL-8, and fibroblast growth factor [11].

The combination of topical IMQ and, for selected lesions, intralesional IL-2, can be utilized to treat patients with accessible melanoma metastases resistant to other treatments [12].

The result is an increase in the mean CD4/CD8 ratio and a rise in the percentage of CD25+ cells in the CD4+ population. Furthermore, staining with activation and T-regulatory markers showed that the majority of this population consists of activated T cells. Cytokine analysis on polyclonally stimulated peripheral blood mononuclear cells showed an increase in the ability of cells to produce interferon (IFN)-gamma over the treatment course, with an initial rise in the IFN-gamma/IL-5 ratio [13].

Another interesting association therapy approach for melanoma metastases was proposed using IMQ and tazarotene topical therapy, with complete clinical clearance of the treated area after a 6-week course [14, 15].

Methods

MEDLINE, EMBASE, Cochrane Library, and Google Scholar databases were searched with the purpose of study selection. The terms "melanoma" combined with "metastases" and "imiquimod" were used as database queries. The only inclusion criterion was: clinical human studies evaluating IMG monotherapy in metastatic melanoma. Any simultaneous combination therapy was excluded. Titles and abstracts were screened by two independent researchers for suitability using predetermined inclusion and exclusion criteria. A modified quality assessment tool for observational studies was used. Data were pooled and analyzed to determine lesion and patient response rates.

Results

Our screening identified 57 studies of which 46 did not meet inclusion criteria, leaving 11 case studies [16-26] summarized in **Table 1**. Heterogeneity was seen in IMQ dosage and treatment interval. Overall, 17 patients were treated in these 11 studies. The main treatment choice was 5% IMQ cream applied once daily (for 6-8 hours), five days per week, under occlusive conditions and this was the regimen used in 8/17 patients (47 %). IMQ was applied 3 times weekly in 5/17 patients (29 %), daily in 2/17 patients (12 %), and twice daily in 2/17 patients (12 %).

Treatment length was variable, with a mean duration of 22 weeks (range 8 - 72 weeks).

Response rate was variable as well. Pooling the lesions, complete regression of melanoma metastases was seen in 82.3% of the patients. One patient required further surgery in order to excise persistent metastases [16]. There was no significant difference in terms of clinical outcome when comparing the frequency of IMQ application.

Treatment was generally well tolerated, with only limited side effects. Localized inflammation, mild pruritus, limited skin breakdown, and episodic mild flu-like symptoms were observed. In a single case the topical treatment regimen was reduced from two applications daily to one application daily, five times per week, owing to an intense inflammation-like reaction in the target area [16].

Table 1. Clinical studies reporting IMQ monotherapy for melanoma metastases

Author(s), Year of publication	Number of patient(s), Gender	Primary Cancer Localization / Age at diagnosis of primary tumor	Metastasis Localization / Age at skin metastases appearance	Treatment	Adverse Effect(s)	Duration of treatment/Outcome
Steinmann A et al.[22], 2000	1, F	Data on location of primary tumor are missing / 50 years old	left breast / 50 years old	5% IMQ cream, 3 times weekly	A local irritation at the treatment sites, typical for IMQ treatment, was the only side effect noted.	18 weeks / Complete regression of tumor cells
Ugurel S et al.[24], 2002	1, M	upper right arm / 81 years old	multiple satellite metastases surrounding the primary excision site / 81 years old	IMQ 5% cream was applied daily under occlusion to the visible metastatic area of 6 cm diameter as well as to a 2-cm margin of surrounding skin.	Only moderate signs of inflammation visible at the treatment site	10 weeks / tumor residues appeared clinically undetectable
Bong et al.[16], 2002	1, F	superficially spreading malignant melanoma located on the right thigh (Clark's level IV, maximum vertical tumor thickness according to Breslow 3 mm) / 80 years old	Right thigh / 82 years old	topical therapy with IMQ 5% cream under occlusive conditions for 6–8 h twice daily	mild flu-like symptoms (headache, fever) superficial erosions and moderate erythema developed at the site of application. moderate, but tolerable pruritus	18 weeks / almost complete resolution (clinically as well as histopathologically) of the lesions. Only 1 cutaneous metastasis persisted and was finally excised at the end of the treatment.
	1, M	superficially spreading malignant melanoma on the left lateral knee (Clark's level IV, Breslow thickness 2.5 mm) / 72 years old	left leg / 73 years old	IMQ 5% cream, two daily applications for 6–8 h under occlusive conditions After an initial intense inflammation-like reaction in the target area :one application daily, 5 times per week.	Over the whole treatment period (now 28 weeks) the strong erythema and erosions persisted, but the patient experienced no other adverse effects.	28 weeks / the pigment lesions disappeared completely. The treatment response was proven by histology. Only 1 cutaneous metastasis showed just little response even after 28 weeks of treatment.
	1, M	nodular malignant melanoma on the left lower leg (Clark's level V, Breslow thickness 5 mm) / 82 years old	more than 25 skin-colored papules of 4–10 mm in diameter arose on the left thigh, knee and around the malleolus lateralis.	IMQ 5% cream, single dose, twice daily for 6–8 h, under occlusion		8 weeks / Metastases had completely disappeared clinically and histologically.
Wolf IH et al.[26], 2003	1, F	malignant melanoma (Clark level IV; Breslow thickness, 1.9 mm) on her right knee / 86 years old	right lower leg / 87 years old	5% IMQ cream, 3 times per week on Monday, Wednesday, and Friday (3 times per week) in the evening and washed off in the morning	mild peritumoral erythema	4months / complete clearing. The patient has been followed up for 15 months without clinical evidence of recurrence.
	1, M	melanoma (Clark level IV; Breslow thickness, 1.8 mm) on the left parietal region of the scalp / 49 years old	retroauricular / 49 years old	5% IMQ cream, 3 times per week on Monday, Wednesday, and Friday (3 times per week) in the evening and washed off in the morning	Superficial scars and residual hyperpigmentation	8 months / complete clearing of the skin lesions
Vereecken P. et al.[25], 2003	1, F	melanoma disease of the left lower leg who relapsed locoregionally after wide excision, elective	Left leg, cutaneous achromic metastases threatened to ulcerate / 67 years old	local IMQ 5% cream, under occlusive dressing for 6 h on 5 days a week.		2 months / the large lesion completely regressed and a control biopsy specimen showed a scar with lymphocytic infiltrate without

		lymph / 57 years old				evidence of residual tumoral tissue
Hesling C. et al.[18], 2004	1, F	chest area / 65-year old	chest and the right axillary region / 76years old	topical IMQ 5% cream, once daily without occlusion		2 months / a dramatic response was obtained with a 90% regression of cutaneous metastases The patient remained in cutaneous partial remission and free from visceral localizations for 2 years but she finally died after melanoma spreading.
Nagore E. et al.[20], 2005	1,F	melanoma 2,6 mm thickness , 3 cutaneous metastases (AJCC IIIC) lower leg / 74 years old	Left lower leg / 74 years old	IMQ 5% cream, 5 days per week		2 months / Progression of the disease - partial regression of some lesions
	1, F	Melanoma 5 mm thickness lower leg / 86 years old	Left lower leg / 88 years old	IMQ 5% cream, 5 days per week	Inflammation and erosion	2 months / regression of some lesions in the first weeks of treatment, then initial lesions remained stable and new lesions appeared on left ankle
Siguenza M. et al.[21], 2005	1, M	Right parietal region, Breslow thickness 4 mm and V Clark / 76 years old	right parietal region / 82 years old	IMQ 5% cream, with 1cm margin of surrounding skin, once daily, 5 days per week	Moderate local erythema	2 months / complete regression
Heber G et al.[17], 2009	1, M	right parieto-occipital region / 63 years old	right parieto-occipital region / 63 years old	IMQ 5% cream, applied once daily for eight hours on five days per week	moderate local side effects consisting of erythema and erosions as the treated site, as well as mild itching and burning.	17 months / complete remission of the cutaneous metastases Four months later, the patient remains free of visceral metastases.
Turza K. et al.[23], 2009	6 One patient is female, data on other patients are missing	a malignant melanoma (superficial spreading type; Clark level III; Breslow thickness 0.75 mm; with regression) on her right anterior scalp / 58 years old	right anterior forehead (4 × 5 cm region located anterior to the previous excision) / 59 years old	IMQ 5% cream, daily for 5 days each week with adjustments made for frequency of application based on individual response and toxicities, five evenings a week to the pigmented area	residual pigmentation	2/6 complete remission after 6 months of treatment 3 did not use the treatment as prescribed one patient had progressive dermal and subcutaneous disease in spite of diligent use
Miller A.K. et al.[19], 2011	1, M	Gastric melanoma / 55 years old	Right iliac fossa and liver / 55 years old	IMQ 5% cream, 3 times per week	Moderate skin breakdown	18 months / Complete regression of liver metastasis and partial regression of right iliac fossa metastasis

Discussion

The aim of our review was to critically assess the studies evaluating the monotherapy with IMQ cream in the treatment of cutaneous metastases from melanoma.

Selection bias and lack of common outcome measures were some of the problems that prevented a proper meta-analysis. Although this review is not a meta-analysis, we critically assessed the literature and tried to identify relevant studies. The main limits of this analysis were the low number of patients included in most of the studies and the high heterogeneity of the patients.

Despite such limitations, the studies analyzed as a whole seemed to demonstrate efficacy of treatment with IMQ in relation to melanoma metastases. Almost complete resolution (clinically and histopathologically) of the lesions was achieved in patients that followed the treatment regimen.

Only Turza *et al.*[23] and Nagore *et al.*[20] reported a negative outcome in some of the patients observed.

The duration of treatment ranged from a minimum of 2 months to a maximum of 17 months, with an average of 7.2 months, ranging from 8 to 72 weeks.

Application frequency ranged from once daily (for 6-8 hours) five days per week under occlusive conditions in 8/17 patients to twice daily in 2/17 patients.

The best responders showed a total or almost total regression of metastases after only two months of therapy [25].

Side effects were limited in the vast majority of cases to local irritation, with the exception of one patient that developed significant inflammation with erosion on the largest application site [20].

Miller A.K. *et al.*[19] provided an interesting finding. Their report shows how the topical application of IMQ has contributed to the regression of liver and internal iliac fossa metastases. In this case the patient used IMQ 3 times per week for a total of 18 months. All other studies concern the treatment of purely cutaneous metastases. In particular, it has been shown that the treatment with IMQ causes regression of dermal lesions but not of the subcutaneous lesions [23].

Conclusions

Treatment of metastatic melanoma with IMQ, which is now second choice if compared with surgical therapy (surgical excision, cryotherapy, laser therapy), should be considered in selected cases. Treatment of metastatic cutaneous melanoma with IMQ cream, used as a single agent, has shown excellent results in terms of efficacy and safety.

However standardized studies are needed in order to objectively evaluate the efficacy of topical therapy with IMQ in melanoma metastases.

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