Defining optimal oncolytic virus treatment and diagnostics in high risk melanoma patients

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CHAPTER 6

Dermoscopy as response evaluation tool for cutaneous malignant melanoma metastases treated with Talimogene Laherparepvec: a prospective feasibility study

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ABSTRACT

Background
Currently, the response of cutaneous melanoma metastases (CMM) to treatment with Talimogene Laherparepvec (T-VEC) is evaluated by clinical examination, macroscopic lesion photography and 3-monthly PET-CT scans. When a complete response (CR) is suspected, biopsies are taken for histopathological confirmation.

Objectives
We set out to investigate the feasibility of dermoscopy in monitoring the response to T-VEC in a pilot study.

Methods
Six patients with CMM treated with T-VEC monotherapy were enrolled in the pilot study. Patients were treated with T-VEC according to protocol and the response was monitored with clinical examination, macroscopic lesion photography and 3-monthly PET-CT scans. For this study, 1-3 cutaneous metastases per patient were selected. Macroscopic and dermoscopic pictures of these metastases were taken at baseline, prior to each treatment with T-VEC and prior to histological biopsy. The pictures were evaluated by two investigators, using a color-based pattern classification.

Results
In total 11 CMM were dermoscopically assessed, 93% was located on the extremities. Four metastases had a blue pattern, two metastases had a pink pattern, three metastases had a brown pattern and two metastases had mixed pattern. Metastases with a pink pattern harbored glomerular and arborizing vessels that diminished and vanished during treatment T-VEC, indicating CR. The remaining metastases did not show changes on a dermoscopic level that were not also seen on macroscopic level. Five patients achieved CR to T-VEC, one patient is still on treatment.

Conclusions
These results suggest that for CMM with a pink pattern, dermoscopy can provide additional information regarding the response to T-VEC. For cutaneous metastases with a blue, brown or a mixed pattern, dermoscopy did not provide additional information on top of the information obtained through physical examination and lesion photography. More studies would be needed to determine the exact role of dermoscopy in the evaluation of CMM.

INTRODUCTION

In recent years, Talimogene Laherparepvec (T-VEC) has been added to the arsenal of treatment options for stage III-IVM1a melanoma, specifically for patients with injectable cutaneous, subcutaneous and/or nodal disease. T-VEC is a genetically modified herpes simplex virus type 1, which mediates anti-tumor activity by directly killing tumors cells and secondarily by promoting a regional and systemic tumor-specific immunity[1, 2]. The phase 3 OPTiM trial treated 436 stage IIIB-IV patients with T-VEC or granulocyte-macrophage colony-stimulating factor and was the first to demonstrate the therapeutic benefit of T-VEC, with an overall response rate (ORR) of 26.4% vs. 6%, respectively. Following this, a subanalysis showed superior results for stage IIIB-IVM1a disease (ORR 40.5% vs. 2%)[3]. Recently, our group was the first to report that the best response rates are seen in the patients with cutaneous metastases, followed by those with subcutaneous and then nodal metastases[4]. This observation was later validated with use of an independent external cohort[5].

In our center, prior to treatment with T-VEC, tumor lesions are clinically assessed by physical examination, macroscopic lesion photography. These evaluation are repeated during treatment, together with a 3-monthly PET-CT scan. Currently, when a complete response (CR) is suspected, punch biopsies are used for histopathological confirmation. Unfortunately, not all cutaneous metastases are easy to assess clinically and therefore it is not uncommon to find residual disease.

Dermoscopy is a noninvasive skin surface microscopy-based tool. It is used for the diagnosis of cutaneous lesions, mainly melanocytic skin cancer but also inflammatory and infectious skin diseases[6, 7]. It has shown to be a valuable tool for monitoring the response by revealing residual disease, adverse events or overuse to various topical treatments[8-10]. This made us wonder if dermoscopy can also be used for evaluating the response of cutaneous melanoma metastases (CMM) treated with T-VEC, allowing a more accurate selection of lesions requiring a biopsy. CMM can vary greatly in their clinical as well as dermoscopic appearance. Only few studies have investigated their dermoscopic features and they all describe different dermoscopic pattern classifications[11-13]. The color-based pattern proposed by Avilés-Izquierdo et al. achieved the highest inter- and intraobserver agreement, describing four demoscopic patterns: blue, pink, brown and mixed[12].

The blue pattern can be defined as homogeneous diffuse monochromatic blue, blue-black or blue-gray pigmentation without any other dermoscopic structures. The pink pattern can be defined as homogeneous diffuse monochromatic pink or reddish pigmentation with irregular/polymorphous vessels in asymmetrical arrangement and/or false red lacunae. The brown pattern can be defined as

homogeneous diffuse monochromatic brown pigmentation with brown dot/globules in asymmetrical arrangement. Lastly, the mixed pattern can be defined as pigmented areas with two or more different colors and any dermoscopic structures, especially peripheral gray spots and/or crystalline structures[12].

With this pilot study, we set out to investigate the feasibility of dermoscopy in monitoring the response of CMM to treatment with T-VEC, using the pattern classification of Avilés-Izquierdo et al.

PATIENTS AND METHODS

This prospective pilot study included patients with histologically confirmed CMM. We enrolled six patients scheduled for treatment with T-VEC monotherapy at the Netherlands Cancer Institute-Antoni van Leeuwenhoek. The study was conducted in accordance with the institutional ethical guidelines. Baseline characteristics were recorded in a database and summarized using descriptive statistics in the Statistical Package for Social Sciences for Windows version 25.0 (IBM).

T-VEC treatment protocol

Patients were treated with T-VEC according to protocol[14, 15]. The first treatment with T-VEC consisted of 10^6 plaque-forming units (PFU)/ml. After three week patients received the second treatment, consisting of 10^8 PFU/ml, which was also the dose they received each 2 weeks thereafter. Blood count, lactate dehydrogenase, tumor marker S100B and infection parameters were assessed by routine laboratory tests every 2 weeks. At each visit, the response of all cutaneous metastases was evaluated by clinical examination and macroscopic lesion photography. Every 3 months a PET-CT scan was performed. 3-mm punch biopsies were used for histopathological confirmation when CR was suspected. Treatment with T-VEC was stopped when patients achieved a CR (either histopathologically confirmed or due to a lack of residual injectable disease), had progressive disease, showed insufficient response or due to toxicities.

Dermoscopic evaluation

For this study, 1 – 3 cutaneous metastases suitable for dermoscopic photography were selected per patient. A dermoscopic as well as macroscopic picture of each metastasis was taken at baseline, every 2 weeks prior to T-VEC treatment and prior to biopsy. Dermoscopic images were captured using a handheld dermatosope attached to a photo camera (Sony A5100).

All dermoscopic pictures were examined by two dermoscopy trained physicians for the presence of dermoscopic features and for the color-based patterns described by Avilés-Izquierdo et al.[12] At baseline the metastases were divided

into four groups based on this classification: blue pattern, pink pattern, brown pattern or mixed pattern. The dermoscopic pictures taken during treatment and prior to biopsy, were assessed for changes.

RESULTS

Eleven CMM on six patients were dermoscopically assessed during treatment with T-VEC. Most patients were male and the median age was 73 years (range 63 – 96). The most common substage was stage IIIC and in 83% of patients the metastases were located on their extremities (table 1).

Five patients had a pathological complete response (pCR) to T-VEC, all within 7 cycles of treatment. For patient 4, histological biopsies were taken after 11 cycles of treatment. Not all metastases showed a histopathological complete response, so his treatment is still ongoing. The metastases that were chosen to assess throughout the treatment, did show a pCR and were therefore included in our analyses.

	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**	**Patient 6**
Age in years, at start T-VEC	70	79	63	96	74	73
Sex	M	M	M	M	M	F
Fitzpatrick skin type	2	2	2	2	2	2
Substage according to the 8th AJCC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIB
Location of metastases	Extremity	Extremity	Trunk	Extremity	Extremity	Extremity
Total number of metastases	+/- 50	+/- 15	+/- 30	+/- 50	+/- 15	1
Number of metastases dermoscopically assessed	2	2	1	3	2	1
Color based patterns (figure)	Blue (1)	Brown (4)	Pink (2)	Pink (3) & Mixed (5)	Blue	Brown
Number of T-VEC cycles	6	7	6	12	4	4
Time to first response in weeks	5	5	3	7	5	7
Time to best response in weeks	13	15	13	On treatment	9	9
Response at end of study	CR	CR	CR	PR	CR	CR

Table 1. *Patient-, tumor- and treatment characteristics. Abbreviations: T-VEC, Talimogene Laherparepvec; AJCC, American Joint Committee on Cancer; CR, complete response; PR, partial response.*

Blue pattern

Four metastases (in patient 1 and 5) had a blue pattern. At baseline, all lesions had monochromatic blue-black pigmentations and no dermoscopic structures (figure 1). No changes in pigmentation or structures were seen during treatment with T-VEC or prior to histological biopsy, irrespective of response.

Clinically, in both patients the metastases became flatter and less palpable. In patient 1, the first 3-monthly PET-CT scan showed a decrease in size and metabolic activity of all lesions. Therefore histological biopsies were taken after 6 cycles of T-VEC. In patient 5, visible clinical changes were the reason to take biopsies after 4 cycles of T-VEC.

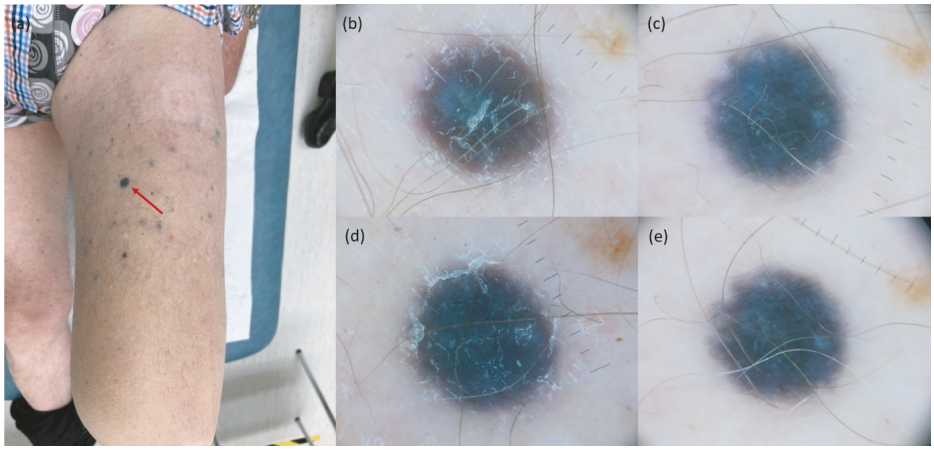

Figure 1. *Metastasis with a blue pattern : (a) macroscopic picture of metastases prior to treatment with T-VEC; dermoscopic picture of metastases prior to- (b) treatment with T-VEC / baseline (c) cycle 2 (d) cycle 6 (e) biopsies, after 6 cycles (15 weeks).*

Pink pattern

Two metastases (in patient 3 and 4) had a pink pattern. All lesions had sharp borders. At baseline, patient 3 had a lesion with irregular and arborizing vessels at the edges (figure 2). During treatment, the pink pigmentation decreased, the vessels diminished and the center began to erode. At baseline, patient 4 had lesions with typical clustered glomerular vessels, looped vessels and linear irregular vessels (figure 3). During treatment, these vessels as well as the lesions itself regressed, decreased in size and they eventually disappeared.

Clinically, metastases of patient 3 became flatter and as some disappeared after 6 cycles of T-VEC, biopsies were taken. Metastases of patient 4 showed a decrease in metabolic activity on PET-CT scan after 6 months. Many of his lesions had

visibly flattened or disappeared after 11 cycles, therefore biopsies were taken. The lesions that were dermoscopically assessed for this study showed a pCR.

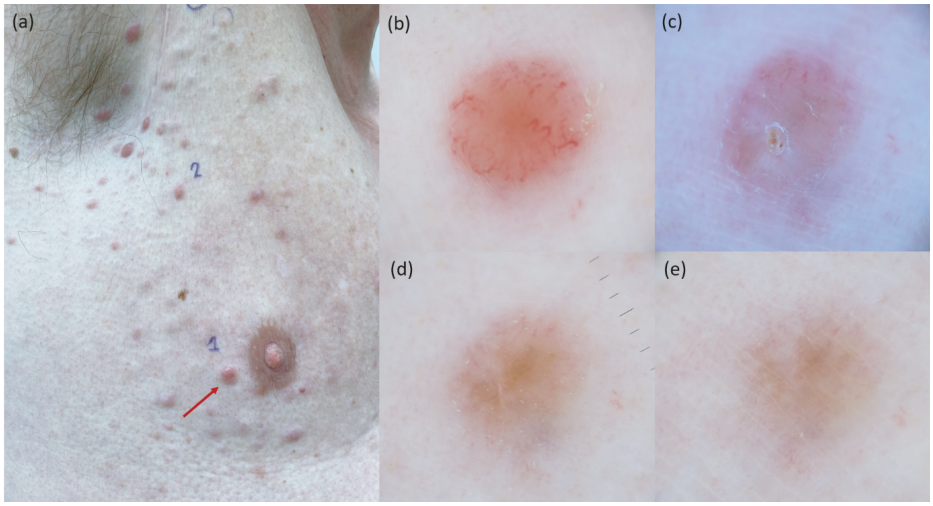

Figure 2. *Metastasis with a pink pattern: (a) macroscopic picture of metastases prior to treatment with T-VEC; dermoscopic picture of metastases prior to- (b) cycle 2 (c) cycle 4 (d) cycle 5 (e) biopsies, after cycle 6 (15 weeks).*

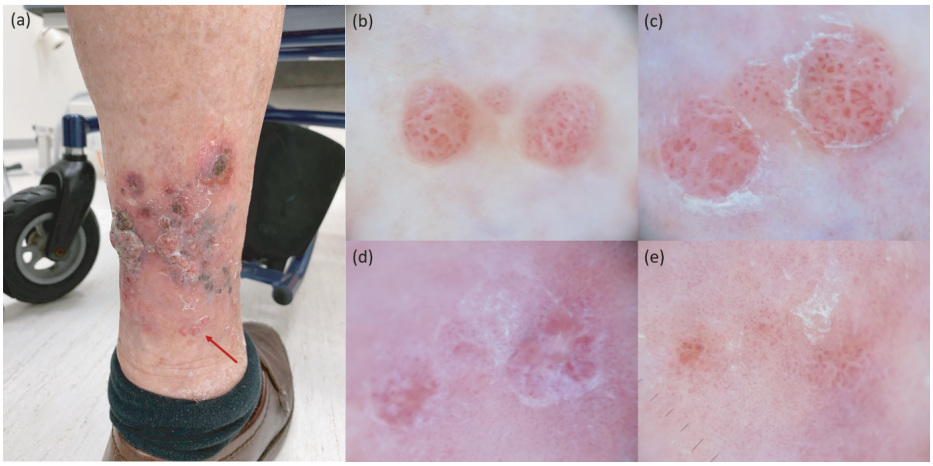

Figure 3. *Metastasis with a pink pattern: (a) macroscopic picture of metastases prior to treatment with T-VEC; dermoscopic picture of metastases prior to- (b) treatment with T-VEC / baseline (c) cycle 2 (d) cycle 4 (e) cycle 7.*

Brown pattern

Three metastases (in patient 2 and 6) had a brown pattern. At baseline, all lesions had sharp borders and brown globules in asymmetrical arrangement (figure 4). No pigment network was observed. During treatment with T-VEC and prior to histological biopsy, the metastases and surrounding skin became increasing erythematous and the globules were no longer seen.

Clinically, metastases of patient 2 became flatter, less palpable and the surrounding skin became erythematous. Biopsies were taken after 7 cycles of T-VEC. Metastases of patient 6 become flatter, but no other macroscopic changes were seen. As this was a single lesion and a quick response was suspected, a biopsy was taken after 4 cycles.

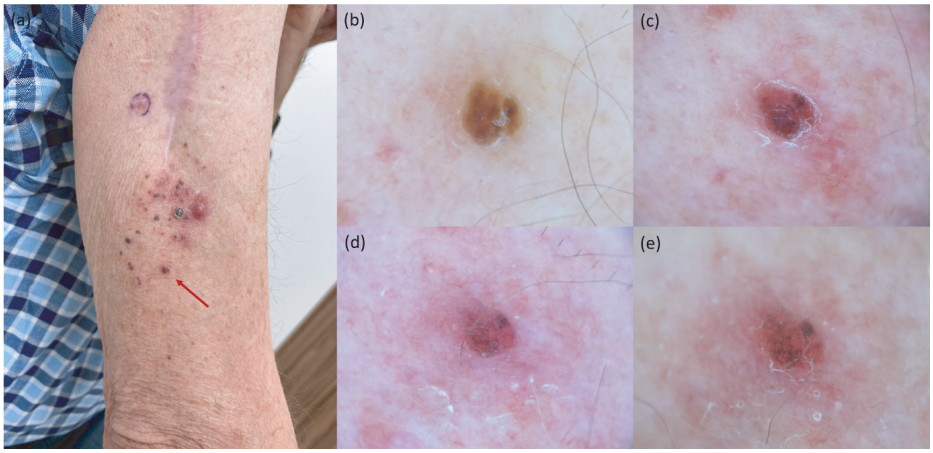

Figure 4. *Metastasis with a brown pattern: (a) macroscopic picture of metastases prior to treatment with T-VEC; dermoscopic picture of metastases prior to- (b) treatment with T-VEC / baseline (d) cycle 4 (d) cycle 6 (e) biopsies, after 7 cycles (17 weeks).*

Mixed pattern

Two metastases (in patient 4) had a mixed pattern. At baseline, the first lesion had a reddish as well as blue-black/blue-gray pigmentation (figure 5). The second lesion had a reddish pigmentation in the center and a purple-black pigmentation at the edges. Both lesions had saccular structures. During treatment, both lesions lost their red pigmentation and regressed.

Metastases of patient 4 showed a decrease in pathological activity on PET-CT after 6 months. Many lesions had visibly flattened or disappeared after 11 cycles, therefore biopsies were taken. The lesions that were dermoscopically assessed for this study showed a pCR.

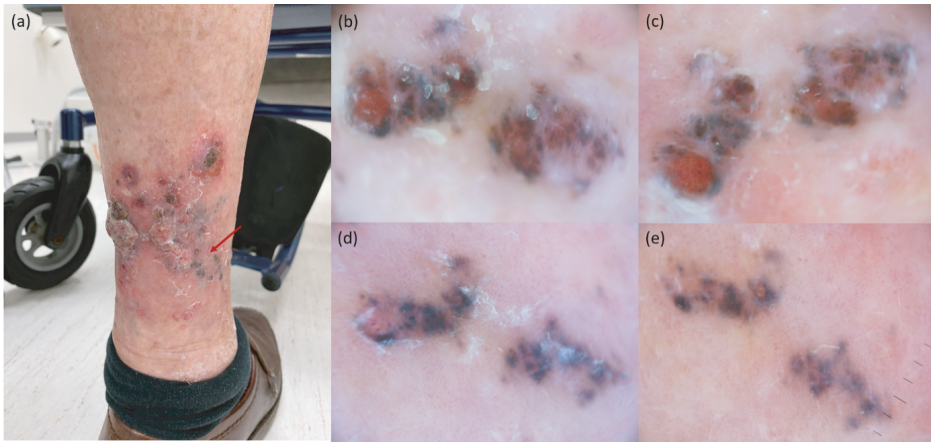

Figure 5. *Metastasis with a mixed pattern: (a) macroscopic picture of metastases prior to treatment with T-VEC; dermoscopic picture of metastases prior to- (b) treatment with T-VEC / baseline (c) cycle 2 (d) cycle 6 (e) biopsies, after 7 cycles (17 weeks).*

DISCUSSION

The advantage of assessing CMM with dermoscopy during treatment with T-VEC, lies in the possibility of more precise timing of biopsy to prove pCR or forego unnecessary futile biopsies in patients who have not yet achieved a pCR. At best, confirmation of a complete response could rely entirely on the dermoscopic assessment, replacing the use of biopsies. It is known that unnecessary biopsies can prolong patient morbidity, leave scars and increase health care costs, so replacing them could benefit patients.

This prospective pilot study is the first to observe the role of dermoscopy as response evaluation tool for CMM during treatment with T-VEC. Dermoscopic pictures taken at baseline, during treatment and prior to biopsy were assessed for dermoscopic structures, using the color-based classification described by Avilés-Izquierdo et al[12]. Metastases with a pink pattern were the only lesions for which we believe dermoscopy can be useful for evaluating the response to T-VEC, as they harbored vascular structures that could not be seen with the naked eye, which faded and eventually disappeared during treatment with T-VEC. Metastases with a blue, brown or mixed pattern revealed either insufficient dermoscopic changes compared to baseline or the changes were also visible by clinical examination.

Although our results only suggest a benefit of dermocopy for melanoma metastases with a pink pattern, clinicians that are inexperienced with T-VEC but do know how to use a dermatoscope, could use our pictures to become more familiar with the different type of melanoma metastases and their microscopic

appearance- and changes during T-VEC. However, in the Netherlands treatment with T-VEC is used by clinicians of the surgical department, who are often inexperienced with dermoscopy. For them a big drawback is the need for formal training to use this tool accurately.

This study has its limitations. It is known that cutaneous metastases of malignant melanoma can adopt various clinical appearances and they can occasionally be confused with other benign or malignant skin conditions[16, 17]. It is likely that we only assessed a part of these appearances, due to the small sample size in this study. Notable is also the success rate of T-VEC in this study: five patients have already achieved a complete response and the sixth patient is still under treatment but has already achieved a partial response (PR). Although a previous study has shown that cutaneous metastases are more likely to achieve a complete response than subcutaneous and nodal metastases, an overall response rate (CR + PR) of 100% is high compared to previous studies[4]. A limitation of these responses is the inability to draw conclusions about the dermoscopic evaluation of CMM that respond partially, do not respond or are progressive on T-VEC. In addition, the differences between responsive and non-responsive metastases cannot be compared.

It is also important to bear in mind that this is an observational study, as the dermoscopic pictures were only taken as an adjunct to all standard treatment procedures and no biopsies were taken for histopathological confirmation of CR, based on these pictures. As this weakens the strength of our conclusions, more research is needed to confidently express the outcomes of this study.

In conclusion, our results suggest that dermoscopy might be of value in monitoring the response of CMM with a pink pattern, as it provides information regarding the response on top of the information already obtained through clinical examination, macroscopic lesion photography and 3-montly PET-CTs. More studies would be needed to determine the exact role of dermoscopy in the evaluation of cutaneous satellite or in-transit melanoma metastases.

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