

ORIGINAL ARTICLES

Experience in the Treatment of Cutaneous In-Transit Melanoma Metastases and Satellitosis With Intralesional Interleukin-2

L.A. Dehesa, J. Vilar-Alejo, P. Valerón-Almazán, and G. Carretero

Servicio de Dermatología, Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria, Spain

Abstract. *Introduction.* Although metastatic melanoma has a poor prognosis, cutaneous metastases represent a special case given their ready accessibility, making it possible for dermatologists to apply local treatment. We report our experience with intralesional treatment with interleukin (IL) 2 in 7 patients with cutaneous metastases from malignant melanoma.

Material and methods. A total of 244 lesions in 7 patients with satellitosis and/or cutaneous metastases from malignant melanoma were treated with intralesional IL-2 twice a week. The maximum dose in each patient ranged from 3 to 18 million units per session, according to the number and size of lesions.

Results. Complete or partial remission was achieved in almost all lesions (95.9% and 3.7%, respectively). Only 1 lesion (0.4%)—the largest and located subcutaneously—did not respond to intralesional treatment and required alcoholization and subsequent surgical removal to achieve cure. All partial responses occurred in subcutaneous lesions larger than 2 cm. Treatment was well tolerated with only a few mild side effects (grade 1-2).

Conclusions. IL-2 may be an effective and well-tolerated treatment option in patients with satellitosis and cutaneous metastases from melanoma. Lesions smaller than 2 cm and located in the epidermis or superficial dermis respond better than those larger than 2 cm or located in the subcutaneous cellular tissue. More studies are necessary to establish appropriate doses and regimens.

Key words: interleukin 2, malignant melanoma, cutaneous metastasis, intralesional therapy.

ESPERIENCIA EN EL TRATAMIENTO DE SATELITOSIS Y METÁSTASIS CUTÁNEAS EN TRÁNSITO DE MELANOMA CON INTERLEUCINA 2 INTRALESIONAL

Resumen *Introducción.* A pesar del mal pronóstico del melanoma metastásico, las metástasis cutáneas constituyen un grupo especial por su fácil accesibilidad que lo hace susceptible al abordaje local por parte del dermatólogo. Describimos nuestra experiencia de tratamiento intralesional con interleucina 2 (IL-2) en 7 pacientes con metástasis cutáneas de melanoma maligno.

Material y métodos. Un total de 244 lesiones en 7 pacientes con satellitosis y/o metástasis cutáneas de melanoma maligno han sido tratadas con IL-2 intralesional administrada dos veces a la semana. Las dosis máximas por pacientes variaron entre los 3 y 18 millones de unidades/sesión, en función del número y tamaño de las lesiones.

Resultados. Se han obtenido remisiones completas (95,9 %) o parciales (3,7 %) en la gran mayoría de lesiones tratadas, una sola lesión (0,4 %), de localización subcutánea y de mayor tamaño, no respondió al tratamiento intralesional y precisó de alcoholización y posterior extirpación quirúrgica para su resolución. Todas las respuestas parciales se observaron en lesiones de localización subcutánea y mayores de 2 cm. El tratamiento fue bien tolerado, con escasos efectos secundarios de intensidad leve (grado 1-2).

Conclusiones. La IL-2 puede ser una buena opción para el tratamiento de pacientes con satellitosis y metástasis cutáneas de melanoma con elevada eficacia y escasos efectos secundarios. Las lesiones menores de 2 cm y localizadas en epidermis o dermis superficial responden mejor que las mayores de 2 cm o localizadas en el tejido celular subcutáneo. Son necesarios más estudios para establecer las dosis y pautas de tratamiento adecuadas.

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Palabras clave: interleucina 2, melanoma maligno, metástasis cutáneas, terapia intralesional.

Correspondence:
Gregorio Carretero Hernández
Servicio de Dermatología
Hospital Universitario de Gran Canaria Dr. Negrín.
Barranco de La Ballena, s/n
35012 Las Palmas de Gran Canaria, Spain
gcarher@gobiernodecanarias.org

Introduction

The treatment of advanced malignant melanoma poses a major challenge to the scientific community of the 21st century, with early diagnosis being crucial to achieving a favorable outcome. The surgical excision of early-stage melanoma has a success rate of close to 100% but no adjuvant therapies have yet proven capable of preventing recurrence in patients with poor prognosis factors. Neither is there any effective treatment for advanced melanoma.

The prognosis for stage III melanoma is generally quite poor, with reported 5-year survival rates ranging from 26% (IIIC, N3) to 69% (IIIA, N1a).¹ Prognosis in patients with stage IV disease is even worse, although it varies greatly depending on the number of metastases and on their size and location. Cutaneous metastases of malignant melanoma, whether locoregional (IIIB/N2c, IIIC/N3) or distant (IV/M1a) are associated with better prognosis and longer mean survival compared to metastases to other organs.^{1,2} Furthermore, because of their greater accessibility, they are detected with greater ease and speed and are therefore more likely to be treated early by a dermatologist.

In recent decades, numerous drugs have been used to treat advanced-stage melanoma, with varying success rates. Nonetheless, the ability of melanoma to induce an immune response and its frequent resistance to chemotherapy and radiotherapy have led to the search for therapeutic solutions capable of regulating the immune system.

We describe our experience over 2 years with the use of intralesional interleukin 2 (IL-2) to treat cutaneous metastases of malignant melanoma in 7 patients.

Materials and Methods

Patients

We treated 7 patients (5 women and 2 men) aged between 59 and 84 years with satellitosis and cutaneous metastases from primary malignant melanoma (5 acral lentiginous melanomas on the lower limb, 1 on the scalp, and 1 superficial spreading melanoma on the trunk). In all, 244 metastases were treated, and over 80% of these (n=202) occurred in a single patient. The remaining 6 patients had a total of 42 lesions between them.

Patient Selection Criteria

The inclusion criteria for treatment were the presence of cutaneous metastases of malignant melanoma or satellite lesions, the absence of metastases to other organs (confirmed by positron emission tomograph [PET] or

computed tomography [CT]), noneligibility for surgical treatment, or failed surgery (recurrences or continued development of lesions) on more than 1 occasion.

Treatment Regimen

In all cases, an aqueous solution containing 18 million international units (MIU) of recombinant human IL-2 (Proleukin) in 6 mL of glucose 5% with albumin (1%) solution was prepared. The solution was divided into 1-mL insulin-type syringes. In an initial session, tolerance was tested by injecting 3 MIU of IL-2 (1 mL of solution) into 1 or 2 of the largest lesions. The dose was divided among the lesions in patients with small lesions only. We followed the recommendations provided by Garbe et al³ in terms of dose per lesion size (0.2 mL, <5 mm; 0.4 mL, 5-10 mm; 1 mL, 10-20 mm; 2 mL, >20 mm), with adjustments for size and treatment response where appropriate. The solution was administered twice weekly (on Tuesdays and Fridays) until clinical resolution of the lesions. In the majority of cases, the frequency of injections was reduced to once weekly in the sessions immediately preceding the complete disappearance of the lesions. All the patients continued to receive treatment for 4 to 6 weeks after the lesions were considered to have resolved both clinically and dermoscopically.

Evaluation of Response

Response to treatment was defined as the clinical and dermoscopic disappearance of treated lesions. We initially performed biopsies to confirm the histologic disappearance of the metastases but once we had gained experience, we decided to simplify the procedure and use just clinical and dermoscopic criteria to modify doses and injection frequency. In all cases, the aim was to treat melanoma and not to perform a validation study of the usefulness of IL-2.

For each patient, we created a progress chart (Table 1) to record and monitor doses, clinical course, laboratory results, and adverse effects.

Case Descriptions

Patient 1

Patient 1 was a 63-year-old woman with no relevant personal history who had been diagnosed with stage IIIA primary malignant melanoma on the sole of the left foot (T3b-N1M0) in December 2005. Following the surgical excision of this tumor and ipsilateral inguinal lymph

node dissection, the patient was administered adjuvant treatment with high-dose interferon- α 2b. Four months later, she presented with multiple millimetric pigmented lesions spread along the entire right lower limb, from the sole to the root of the thigh (Figures 1A and 1B). A biopsy of 1 of the lesions confirmed the presence of malignant melanoma metastasis. Completion of staging evaluation using a full-body CT scan revealed the absence of other metastases. Several treatment options were considered. Among these, perfusion of the affected leg with melphalan and tumor necrosis factor (TNF)- α was ruled out because the lesions extended beyond the perfusion area of the leg and we had little experience with this treatment at our hospital. We finally opted to initiate treatment with intravenous paclitaxel and intralesional IL-2. The maximum daily dose of IL-2 was 18 MIU, injected twice a week into 202 millimetric pigmented lesions spread along the left lower limb (Table 2). The patient tolerated the treatment well. The only significant side effects observed were fever, chills, and muscle pain. They appeared within 4 to 6 hours of the administration of IL-2 but subsided with the administration of antipyretics. After 4 weeks of treatment, several lesions started to develop an achromic halo. They later formed ulcers and ultimately disappeared completely. On observing the halos, we decided to biopsy 4 lesions of different stages (Table 3 and Figure 2). The lesions disappeared after 18 weeks of treatment, leaving just slight residual hypopigmentation (Figures 1C and D). One larger dermal-hypodermal lesion measuring 4 × 4 cm in the inguinal region, next to the lymphadenectomy scar, did not respond to intralesional treatment and required alcohol injection and subsequent surgical removal. Six months after the end of treatment and the complete remission of all the skin lesions, the patient developed multiple metastases to the liver and lungs. She died 3 months later, despite systemic treatment with temozolomide and bevacizumab. In total, the patient received 553 MIU of IL-2 over 38 weeks.

Patient 2

Patient 2 was a 76-year-old man diagnosed with malignant melanoma of the scalp and right temporal region with satellite lesions in May 2006. The skin lesions were surgically removed and a biopsy performed on the sentinel lymph nodes, 2 of which were found to be infiltrated by malignant melanoma (one in the retroauricular region and the other in the cervical region). Subsequent dissection of the cervical lymph node chain and the ipsilateral retroauricular area showed no involvement in the 34 nodes examined. A full-body CT scan and PET performed at the time to screen for disease spread was also negative (stage IIIC [T3b-N3M0]). The patient was started on

adjuvant therapy with high-dose IFN α 2b. One month later, he presented with a pigmented lesion of recent onset measuring 0.5 cm in the right temporal region, next to the top border of the excision scar. Biopsy confirmed the presence of malignant melanoma metastasis. Subcutaneous IFN treatment was continued for 4 months, until the patient developed 4 new pigmented punctuate lesions contiguous to the scar. Metastasis of malignant melanoma was also confirmed by biopsy in these cases. Treatment with IFN was stopped and a new staging evaluation confirmed the absence of other metastases. It was decided to initiate treatment with oral temozolomide. In the following 4 months, 18 millimetric pigmented lesions consistent with melanoma metastases were removed from the patient. At that point, considering the poor response to systemic chemotherapy and the absence of metastases to other organs, it was decided to initiate treatment with intralesional IL-2 based on a regimen of 3 MIU injected twice a week into all clinically identifiable lesions. In total, 16 millimetric pigmented lesions located on and adjacent to the skin graft scar were treated (Figure 3A). Complete remission was achieved for all the lesions after 14 weeks of treatment. The injections were continued for 6 weeks after clinical resolution of the lesions. The patient tolerated the treatment well. The only adverse effect observed was flu-like syndrome with general malaise. The symptoms appeared approximately 8 hours after treatment and resolved with the administration of oral paracetamol. Not only did all the lesions treated disappear but no new pigmented lesions have appeared in the 6 months since treatment ended (Figure 3B). In total, the patient received 90 MIU of IL-2 over 20 weeks.

Patient 3

Patient 3 was a 68-year-old woman diagnosed, in May 2007, with stage IB malignant melanoma of the right breast with negative sentinel lymph nodes (T2aN0M0). Seven months later, she suddenly developed 6 millimetric pigmented lesions (the largest of which measured 0.8 cm in diameter) around the surgical scar on the breast. Histopathology confirmed a diagnosis of satellite lesions of melanoma (Figure 4A). Staging evaluation was negative for additional metastatic disease and the melanoma was reclassified as stage IIIB (T2aN2cM0). As in the first 2 cases described, patient 3 also received palliative care based on a treatment regimen of 6 MIU of IL-2 injected into the 8 metastatic lesions twice a week. She tolerated the treatment well, except for pain and a local burning sensation in the hours following the administration of the drug. She also experienced low-grade fever but this was controlled with paracetamol at standard doses. Response to treatment was excellent.

Table 1. Treatment Monitoring Chart for Interleukin 2

Name						
Diagnosis		Tel. No.		Patient History		
Inclusion Criteria	Assessments	Baseline	Week 1	Week 2	Week 3	
Cutaneous or subcutaneous melanoma metastases	Date: ___/___/___					
	Examination					
	No. of metastases treated					
	Chest radiograph					
Main toxicity	Blood pressure, mm Hg					
– Hypotension – Confusion – Arrhythmia – Oliguria	Urea/creatinine, mg/dL					
	Blood count	Leukocytes, 10 ³ /mL				
		Neutrophils, 10 ³ /mL				
		Lymphocytes, 10 ³ /mL				
		Hemoglobin, g/dL				
Contraindications	Platelets, 10 ³ /mL					
Absolute contraindications – Allergy to drug – Pregnancy, breastfeeding – Severe infections	Bilirubin, mg/dL					
	AST/ALT, U/L					
	LDH/ALP, IU/dL					
	Cl/Na/K, mEq/L					
Relative contraindications – Liver failure – Kidney Failure – Pulmonary insufficiency – Edema – Bleeding						
	S-100B/MIA					
	ECG (repeat depending on clinical condition)					
	Adverse reaction					
	*					
	Visit with nurse	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	Visit with physician	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other drug-related reactions and effects (see over)	Daily dose Cumulative dose (weight) =					

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECG, electrocardiogram; LDH, lactate dehydrogenase; MIA: melanoma inhibitory activity.

Six weeks after the first injections, the lesions started to form ulcers. They then developed a crust and by week 12 had disappeared completely (Figure 4B). At the time of writing, the patient has been without treatment for 1

month. She is in complete remission, with no signs of recurrence and no metastases detected by full-body CT. In total, the patient received 90 MIU of IL-2 over 15 weeks.

Table 2. Summary of Clinical Data and Patient Outcome

Patient	Sex	Age, y	Location of Primary MM	Breslow Thickness, mm	SLN Study	Time to Metastasis, mo	No. of Metastases	Metastases <5 mm, No.	Metastases 5-10 mm, No.	Metastases <10 mm, No.	No. of Sessions
1	F	63	Sole of left foot	1.44	+	9	202	191	9	2	64
2	F	76	Scalp	NA (Clark IV)	+	4	16	16	0	0	30
3	F	68	Right breast	1.3	(-)	5	8	6	2	0	20
4	F	84	Left leg	2.5	(-)		3	0	3	0	22
5	F	59	Left foot	Metastasis	NA	0	8	0	1	7	25
6	F	84	Left leg	4.12	+	1	6	4	2	0	20
7	F	71	Left ankle	6.0	ND	600	1	0	0	1	27

Abbreviations: +, positive; (-), negative; BZM, bevacizumab; NA, not available; ND, not done; SLN, sentinel lymph node; TMZ, temozolomide; WHO, World Health Organisation.

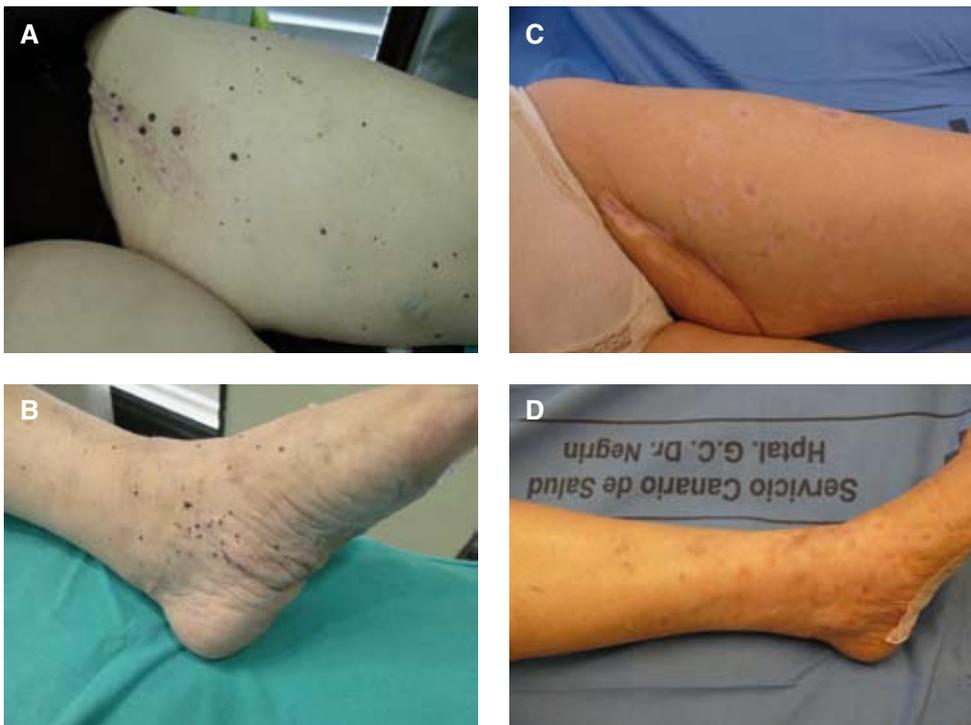


Figure 1. Patient 1. A and B, leg before treatment with intralesional interleukin 2. C and D, leg after treatment.

<i>Duration, wk</i>	<i>Cumulative Dose, MIU</i>	<i>Achromia</i>	<i>Adverse Effects (WHO Classification)</i>	<i>Visceral Metastases</i>	<i>Associated Treatment</i>	<i>Time Since Onset of Metastases, mo</i>	<i>Current Situation</i>
38	553	Around treated lesions	Fever, flu-like syndrome, local pain	+	TMZ, BZM, surgery	13	Complete remission of cutaneous metastases. Died after 13 months due to spread of malignant melanoma to organs.
20	90	–	Fever, flu-like syndrome	–	TMZ	24	Alive, free of disease, without treatment for 6 months.
15	90	–	Fever, flu-like syndrome, pain, dysgeusia	–	–	7	Complete remission, free of disease, without treatment for 1 month.
18	66	–	Fever, local infection	–	–	6	Alive, receiving treatment, no signs of disease.
16	98	Distant vitiligo	Fever, flu-like syndrome, bronchospasm.	–	Surgery	6	Alive, receiving 6 MIU twice a week, no clinical evidence of lesions. Negative for other metastases.
13	120	–	Lymphangitis, flu-like syndrome	–	–	5	Alive, receiving treatment with 6 MIU/week, lesions at crusting stage. Negative for other metastases.
17	81	–	Flu-like syndrome	–	Surgery	38	Alive, free of disease, without treatment for 18 months.

Table 3. Correlation Between Clinical and Histopathologic Features of Cutaneous Lesions of Different Stages in Patient 1

<i>Lesion</i>	<i>Clinical Description</i>	<i>Histopathologic Description</i>
1	Metastatic lesion of recent onset on left muscle before treatment with intralesional interleukin 2 (IL-2) (Figure 2A).	Histopathology showed the presence of nests of melanocytes in the superficial dermis with abundant mitosis, confirming the presence of metastasis of melanoma (Figure 2a).
2	Pigmented lesion (visibly persistent) surrounded by hypopigmented halo on inner side of left thigh after 4 weeks of treatment with intralesional IL-2 (Figure 2B).	Histopathology showed an intratumoral and peritumoral infiltrate with necrotic tumor tissue and melanophages. There were also some eosinophils but no viable tumor cells (Figure 2b).
3	Ulcerated lesion (not visibly persistent) surrounded by hypopigmented halo on inner side of left thigh after 4 weeks of treatment with intralesional IL-2 (Figure 2C).	Histopathology showed an even denser lymphocytic infiltrate than in lesion 2, with abundant melanophages but no viable tumor cells (Figure 2c).
4	Pigmented lesion (visibly persistent) without hypopigmented halo on inner side of left foot after 4 weeks of treatment with intralesional IL-2 (Figure 2d).	Less dense lymphocytic infiltrate in the superficial dermis than in earlier lesions but also without viable tumor cells by both hematoxylin-eosin staining or immunohistochemical staining with S-100 or HMB45 (Figure 2D).

IL-2: interleucina 2.

a hypochromic nodular lesion under the surgical scar. The lesion was removed and histologic analysis confirmed metastasis of melanoma. No evidence of metastatic disease was detected in the staging evaluation performed

at the time and the disease was reclassified as stage IIIB (T3aN2cM0). In the weeks that followed, similar lesions continued to appear around the scar, prompting treatment with intralesional IL-2 based on a twice-weekly regimen of

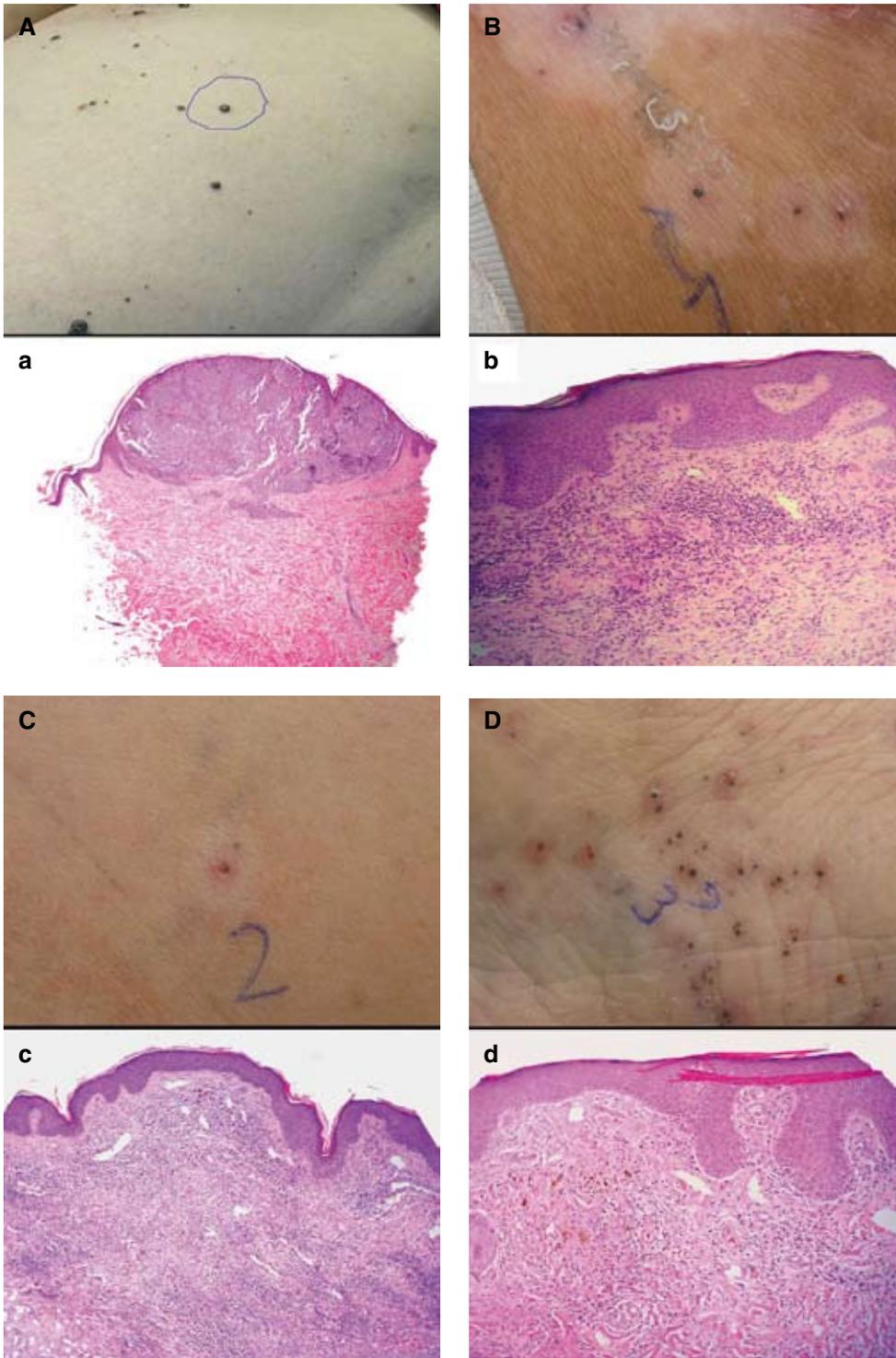


Figure 2. Patient 1. Correlation between clinical and histopathologic findings. A, metastatic lesion on left thigh before treatment with interleukin 2 (IL-2); a, histologic appearance of lesion A (hematoxylin-eosin, $\times 100$); B, pigmented lesion on inner side of left thigh surrounded by hypopigmented halo after 4 weeks of treatment with IL-2; b, histologic appearance of lesion B (hematoxylin-eosin, $\times 400$); C, ulcerated lesion on left thigh surrounded by hypopigmented halo after 4 weeks of treatment with IL-2; c, histologic appearance of lesion C (hematoxylin-eosin, $\times 200$). D, pigmented lesion on inner side of left foot surrounded by hypopigmented halo after 4 weeks of treatment with IL-2; d, histologic appearance of lesion D (hematoxylin-eosin, $\times 400$).

3 to 6 MIU per session, divided among 3 lesions. The patient tolerated the treatment well but during the sixth week he developed a skin infection in the injection area requiring suspension of treatment for 10 days and the administration of broad-spectrum oral antibiotics (amoxicillin and clavulanic acid). Treatment was reinitiated and no other

adverse effects of relevance were observed. The treatment period (18 weeks) was completed a week before the time of writing. The patient's lesions have disappeared completely and a full-body CT scan has confirmed the absence of metastatic disease. In total, the patient received 66 MIU of IL-2 over 18 weeks.

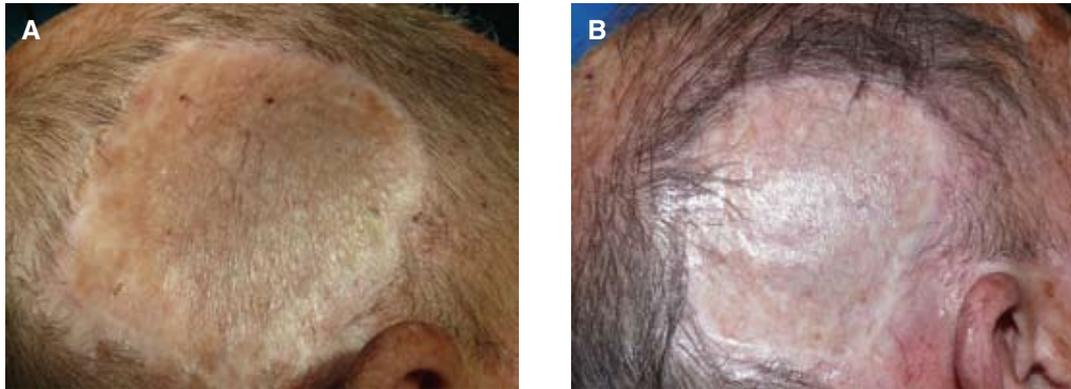


Figure 3. Patient 2. A, before treatment with interleukin-2 (IL-2). Note the millimetric pigmented lesions around and near the graft; B, after treatment.

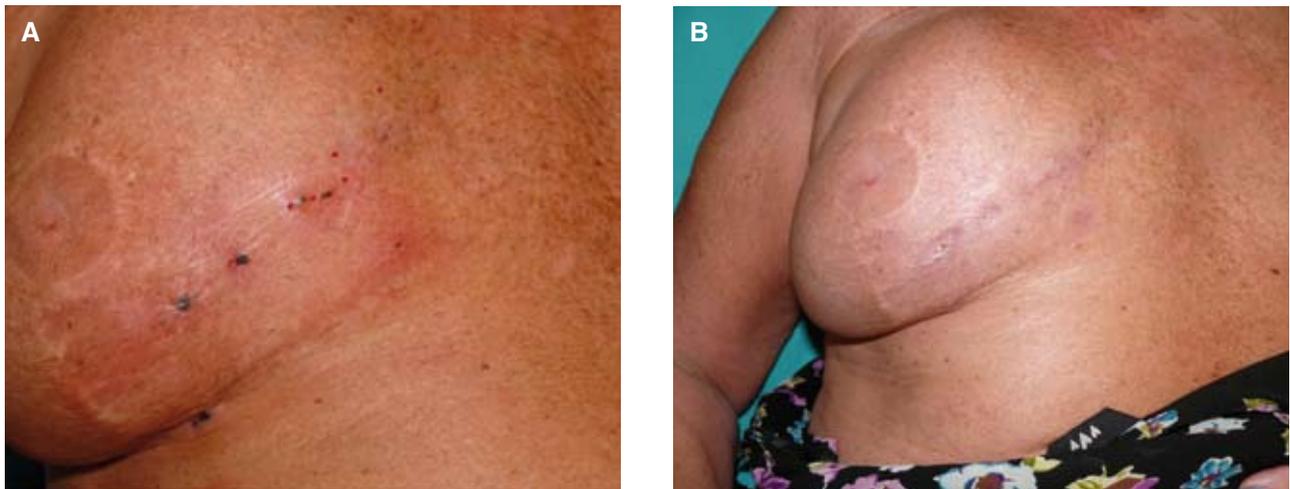


Figure 4. Patient 3. A, lesions before treatment with intralesional interleukin 2. B, after treatment.

Patient 5

Patient 5 was a 59-year-old woman with a history of bronchial asthma, cervical arthrosis, and nail disease in the first toe of her left foot. The nail disease had started several years earlier and had required the partial or complete removal of the nail on several occasions by the patient's podiatrist. In January 2008, the patient started to develop multiple dermal-hypodermal nodules along the lower left limb, stretching from the dorsum of the foot to the groin. A biopsy of 1 of the lesions confirmed metastasis of malignant melanoma (stage IIIC [TxN3M0]).

The site of the primary tumor is unknown but it was probably subungual. PET confirmed the presence of 8 nodular lesions along the lymph node chain of the left lower limb but there were no signs of metastases to other sites. It was decided to start intralesional treatment with IL-2 administered twice a week at a dose of 9 MIU per session divided among all the lesions. After 4 weeks of treatment, it was decided to remove all 8 lesions following confirmation that the lesions had reduced in size and that no new lesions had appeared. In all 8 cases, histopathology confirmed metastasis of malignant melanoma with intense intratumoral and peritumoral

inflammatory infiltrates and extensive necrosis within the tumor and in the surrounding adipose tissue. Three weeks later, a new pigmented lesion developed in the periungual area of the nail of the first toe on the left foot and it was decided to restart treatment with intralesional IL-2 at a daily dose of 3 MIU twice a week. The patient tolerated the treatment well, experiencing just local pain during the administration of the drug and low-grade fever several hours later. On 2 occasions, the patient experienced bronchospasm during administration. It is also noteworthy that the patient developed symmetrical achromic lesions on both shoulders after 12 weeks of treatment. These lesions were clinically diagnosed as vitiligo. At the time of writing, the patient is still receiving treatment twice a week with 6 MIU of intralesional IL-2. The lesions have clinically remitted and no new lesions have appeared. A full-body CT scan performed a week ago confirmed the absence of metastases to other sites. The patient has received 98 MIU of IL-2 over 16 weeks.

Patient 6

Patient 6 was an 84-year-old woman who had had an ulcerated malignant melanoma with a Breslow thickness of 4.12 mm removed from the left pretibial region in January 2008. The surgical defect was covered with a

split-thickness skin graft and the sentinel lymph node study was negative. A left inguinal lymphadenectomy was performed in which 7 of the 11 lymph nodes dissected were found to be positive for metastasis of malignant melanoma (stage IIIC [T4bN3M0]). At that moment, the patient and her family chose to not continue with systemic treatment to control the disease. In subsequent visits, we observed the progressive appearance of millimetric pigmented lesions contiguous to and at some distance from the graft (Figure 5A). The lesions were clinically consistent with melanoma satellite lesions, a diagnosis that was confirmed following the biopsy of 1 of the lesions. A full-body CT scan taken at the time was negative and palliative treatment with intralesional IL-2 was initiated at a twice-weekly dose of 3 to 6 MIU per session divided evenly among 6 skin lesions located around the surgical graft. The patient tolerated the treatment well. The only significant adverse effects observed were edema and erythema in the affected leg. Doppler ultrasound of the left leg was performed to monitor for proximal deep vein thrombosis. The results of this examination revealed lymphangitis and seroma secondary to the lymph node dissection. The patient is currently in the 13th week of treatment and receiving 6 MIU of IL-2 once a week. All the skin lesions have formed a crust (Figure 5B) and there was no evidence of metastasis in the latest full-body scan. To date, the patient has received 120 MIU of IL-2 over 13 weeks.

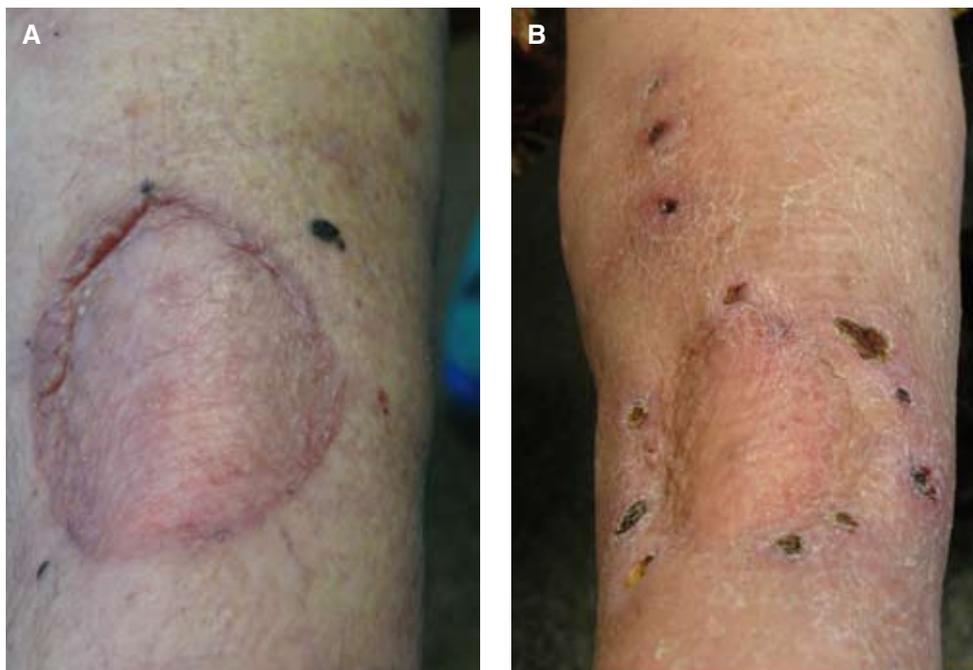


Figure 5. Patient 6. A, lesions before treatment with interleukin 2 (IL-2). B, lesions during crusting phase during treatment with IL-2.

Patient 7

Patient 7 was a 71-year-old woman diagnosed with malignant melanoma of the left ankle in March 2000. The tumor, which had a Breslow thickness of 6 mm and was deeply invasive (Clark level V), was classified as stage IIB (T4aN0M0). Five years later, she presented with a nodule measuring 3 × 2 cm in diameter in the left inguinal region. The nodule was removed but the melanoma was found to have spread to and beyond the lymph nodes, with a mass of enlarged lymph nodes (stage IIIC). The patient was treated with high-dose INF- α 2b. Eight months later, she presented a new deep-seated subcutaneous indurated nodular lesion measuring 4 × 3 cm in diameter on the inner side of the left knee. A full-body CT scan ruled out other distant metastases. The patient refused to undergo surgery and/or systemic chemotherapy but finally agreed to receive treatment with intralesional IL-2. After 4 months, in which she was administered 3 MIU of IL-2 twice a week and experienced only slight adverse effects (fever and joint pain coinciding with the administration of the drug but subsiding within a few hours with the administration of 500 mg of oral paracetamol), the size of the lesion had decreased considerably and it was decided to remove it surgically. Histopathology confirmed metastasis of malignant melanoma with a considerable inflammatory reaction and necrosis. Eighteen months later, at the time of writing, the patient is no longer on treatment and is in complete remission, with no signs of disseminated disease. In total, she received 81 MIU of IL-2 over 17 weeks.

Discussion

The intralymphatic spread of melanoma causes the appearance of satellite lesions and metastases along the pathway from the primary tumor to the regional lymph nodes. Prognosis in such cases is independent of the number of lesions present and is invariably grim, with an estimated 5-year-survival rate of 53% if there is no regional node involvement (stage IIIB) and of 26% if there is (stage IIIC).^{1,4} The incidence of lymphatic spread varies from 1% to 19% depending on the series,^{1,5} with most cases (up to 70%) affecting the lower limbs.⁶ In our series, 5 patients developed metastases of the legs, 1 of the trunk, and 1 of the scalp.

Diverse treatments have been used in patients with in-transit metastases and satellite lesions, including systemic chemotherapy, immunotherapy, radiotherapy, surgery, isolated limb perfusion with biotherapy or chemotherapy agents, intralesional injections of different drugs and therapeutic agents, and local destructive procedures such as cryotherapy, electrofulguration, carbon dioxide laser therapy, and electrochemotherapy.^{7,8}

Response to the majority of treatments is very poor, with very little impact on overall survival. Isolated limb perfusion with TNF- α and melphalan is, perhaps, the approach that offers the best results, particularly in patients with large or highly aggressive regional metastases.⁹ The method is not widely used, however, first, because it is suited only to certain clinical situations, and second, because it requires a certain degree of skill and technique not always available in departments treating these cases.^{10,11} Patients 1 and 5 in our series would have been candidates for this treatment, but, for reasons already mentioned, this was not possible. From among the more feasible alternatives available, we chose the intralesional injection of IL-2. In our opinion, our patients met the eligibility criteria and the approach has demonstrated high response rates with few significant adverse effects.³

IL-2 is a glycoprotein that was described in 1976 as a T cell growth factor.¹² Structurally, it is a lymphokine of 133 amino acids, comprises a bundle of 4 helices, and is encoded by a single gene at chromosome 4q26.¹³ It is secreted mainly by activated helper T cells but also by CD8⁺ lymphocytes and dendritic cells.

It plays a key regulatory role in the immune system by stimulating the cytotoxicity of T cells and natural killer cells and acting as a cofactor in the activation of B cells and macrophages.^{14,15} It acts by stimulating the IL-2R receptor, a transmembrane receptor formed by 3 protein subunits. The intracytoplasmic domain of this receptor is associated with a series of protein kinases from the Janus kinase (JAK) family (JAK 1, JAK 3). When stimulated by the ligand, the receptor undergoes a conformational change, causing the phosphorylation of the associated protein kinases, which, in turn, activate each other and stimulate another group of cytoplasmic proteins belonging to the signal transducer and activator of transcription family. Following stimulation by activated JAKs, these transcription factors dimerize and translocate to the nucleus, where they act directly on DNA, promoting the expression of certain genes that intervene in the inflammatory response.^{14,16}

IL-2 was approved for the treatment of renal cell carcinoma in 1992 and for malignant melanoma in 1998.¹⁷ It has been tested clinically in multiple doses and using varying routes including intravenous administration,¹⁸ inhalation,¹⁹ and intralesional injection.³ Intravenous administration has achieved response rates of close to 20% but its main limitation, which prevents the use of appropriate doses in many patients, is the high toxicity associated with this route. One of the main adverse effects associated with intravenously administered IL-2 is the capillary leak syndrome, which is an accumulation of liquid in extravascular spaces caused by an increase in capillary permeability induced by IL-2. This syndrome can result in generalized edema, weight gain, hypotension,

tachycardia, lung congestion, oliguria, renal failure, and death.¹⁵ The main advantages of the intralesional administration of IL-2 are that it is highly effective and that it is associated with few and mild adverse effects.³ This is possible because high concentrations of drug are delivered to the tumor using much lower doses than those required intravenously.

All of our patients achieved complete or partial remission, confirmed by clinical and dermoscopic findings in the majority of cases and histological findings in some (see Methods), and none of them experienced significant adverse effects. Just 1 subcutaneous lesion which, with a diameter of 4 × 6 cm, was larger than the rest, did not respond to treatment and required alcohol injection and subsequent surgical excision.

The most common adverse effects experienced by the patients in our series were fever, chills, and joint pain several hours after the injection of IL-2. These symptoms, however, did not impede activities of daily living and disappeared on treatment with analgesics or antipyretics. Other effects observed included pain at the injection site, vomiting, local infection, superficial lymphangitis, and bronchospasm. Contrasting with previous findings,²⁰ none of our patients experienced neurologic or psychologic changes. It is particularly interesting to note that all of the adverse effects recorded in our series were mild to moderate (grades 1 and 2) according to the criteria established by the latest version of the Common Terminology Criteria for Adverse Events of the National Cancer Institute.²¹

Just 1 patient (patient 1), without a personal or family history of vitiligo or Sutton's halo nevus, developed an achromic halo around many of the lesions treated. Patient 5 developed symmetrical achromic lesions, diagnosed as vitiligo, on both shoulders during the 13th session. The development of vitiligo in association with melanoma or in response to the treatment of melanoma is not unknown and has been related to improved prognosis or treatment response,²²⁻²⁶ suggesting an association with an immune response induced by treatment targeting antigens shared by melanoma cells and normal melanocytes.^{27,28} Interestingly, in the case of patient 1, the halo appeared before the lesions disappeared, possibly supporting the above theory. Nonetheless, lesions that were not surrounded by a halo also disappeared at the same time. While this finding is of theoretical interest, it has little practical value. Histopathologically, the lesions surrounded by the halo had a dense intratumoral and peritumoral lymphocytic infiltrate with necrotic tumor tissue, melanophages, and some eosinophils. There was, however, no evidence of viable tumor cells by either hematoxylin-eosin staining or immunohistochemical staining with S-100 or HMB45. The lesions not surrounded by a halo did

not have viable tumor cells either; they did have an intratumoral and peritumoral infiltrate but this was much sparser.

Optimal doses for the intralesional administration of IL-2 have not yet been established. In our series, the doses ranged from a minimum of 3 MIU/day (patient 2) to a maximum of 18 MIU/day (patient 1), with dose adjustments made in accordance with the number and size of lesions. The maximum dose administered per lesion was 6 MIU. We performed the injections twice weekly until the lesions disappeared completely. We followed a highly flexible regimen, in which both doses and injection frequency were reduced as the lesions gradually disappeared.

It seems to be accepted that treatment response does not depend on the number or the time since onset of the lesions but rather on their size and histological localization, with smaller lesions located in the epidermis and/or superficial dermis responding better than lesions larger than 2 cm located in the subcutaneous tissue.^{3,29} Our findings support such reports as in our series, both larger lesions and lesions located in subcutaneous tissue responded more slowly or only partially to treatment. Indeed, in patients 1 and 7, both of whom had large lesions, the injection of IL-2 caused central (nuclear) metastatic inflammation, with subsequent necrosis and lesion cavitation. The lesions, however, did not disappear and had to be removed surgically. Patient 7 had a single lesion on the inner side of the left knee but surgery was ruled out due to the risk of collateral damage to the bones and tendons of the knee. The lesion became necrotic and cavitated with the repeated injection of IL-2 but it did not disappear. It did, however, decrease in size, allowing it to be successfully excised. At the time of writing, 7 years after diagnosis including 3 at stage IIIC, the patient is still free of disease.

Surgical excision is evidently the treatment of choice for patients with few local or in-transit metastases. We believe, however, that intralesional IL-2 is a much simpler approach for multiple lesions. (Patient 1 in our series, for example, initially had over 100 lesions.) Intralesional IL-2 would also seem to be the treatment of choice in patients with primary melanoma of the leg or the sole as such tumors frequently produce multiple metastatic lesions. (Patients 1 and 2 developed consecutive multiple metastatic lesions that were removed on various occasions before treatment with intralesional IL-2.) Furthermore, as explained in the previous paragraph, small lesions seem to respond better to treatment.

The choice of treatment is not so clear, however, when visceral or distant metastases are involved as the results of numerous studies suggest that the

intratumoral administration of IL-2 acts only at a local level, with no measurable systemic effect.^{3,30} We do not, however, entirely agree with this view. Although in our series, we did not observe any distant effects that were attributable to the local administration of IL-2—we saw no evidence of regression of untreated concomitant metastases (only clinically identifiable lesions were treated)—we presume that there must be some type of systemic or at least locoregional effect, as prior to treatment, patient 2 had developed multiple consecutive cutaneous metastases (28 removed over a period of 4 months). Now, 8 months after initiation of treatment with intralesional IL-2, all the metastases treated have disappeared and no new ones have appeared. Furthermore, we believe that the distant vitiligo observed in patient 5 after 12 weeks of treatment was the result of the systemic activity of intralesional IL-2.

Nonetheless, and even in patients with stage IV disease and multiple metastases, the possibility of using intralesional IL-2 in combination with another palliative treatment cannot be ignored given the fact that the treatment eliminates skin lesions and that this has an enormously positive effect on patients. The ideal candidates for the intralesional injection of IL-2 are patients with in-transit lesions only, few visceral metastases, or metastases that remain stable, such as stage M1b lung metastases, which could also be treated with inhaled IL-2.³¹

We would like to highlight the fact that 4 of the 7 patients in our series (patients 2, 3, 4, and 7) achieved complete remission and are currently receiving no treatment. The longest duration of remission to date is 18 months (patient 7). Patients 5 and 6 are still receiving treatment but the lesions treated have completely disappeared and no new metastases have been detected. Finally, although patient 1 responded well to local treatment (complete resolution of all skin lesions), she developed multiple visceral metastases, obliging us to suspend intralesional IL-2 treatment and initiate systemic chemotherapy.

While the theoretical aim of treating metastatic melanoma is to achieve complete response, lesser goals, such as partial response or disease stabilization, above all in patients with concomitant or consecutive locoregional in-transit and disseminated metastases, can be achieved with relative ease. The use of low-dose IL-2 in combination with other drugs such as temozolomide and granulocyte-macrophage colony-stimulating factor holds great promise, as has been reported by several authors.³²⁻³⁵ Patients 1 and 2 in our series received concomitant treatment with intralesional IL-2 and oral temozolomide, with patient 2 continuing the oral medication after completion of the intralesional IL-2 treatment period. One recent proposal for the treatment

of melanoma metastases, based on the findings of a clinical trial, is the combined use of topical imiquimod with intralesional IL-2, with the continued injection of intermediate-dose IL-2, even after the disappearance of lesions.³⁶ In a later study, the same group showed that this combination could potentially induce systemic immunologic effects.³⁷ The use of intermediate, serial doses of IL-2 is another promising strategy, albeit one that needs to be validated. In view of the fact that there is no cure for melanoma, the use of “minor” immunologic interventions, either in combination or succession appears to be a valuable, practical, and nonaggressive strategy in the palliative management of this disease.

We have described our experience with the treatment of 244 lesions in 7 patients with in-transit metastases and satellite lesions of cutaneous malignant melanoma using intralesional IL-2 injections. Particularly worthy of mention is the good response obtained in all cases and the importance of starting treatment before the first in-transit metastases appear due to the better results seen with small lesions. Optimal doses and the impact of these on overall survival remain to be determined, although we believe that they play an important role in disease stabilization. The potential systemic effect of intralesional IL-2, administered either alone or in association with other immunomodulatory or chemotherapy molecules, also remains to be elucidated.

Conflicts of Interest

The authors declare no conflicts of interest.

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