Imiquimod 5% cream in occlusion, for the treatment of lentigo maligna: a new scheme of short cycles and the need for clinical trials

Stefano Astorino,MD;[1] Paolo Astorre,MD;[2] Paola Pasquini,MD;[3]Donato Di Nunno,MD;[1] Federico Pellegrini,MD;[2]Giovanni Paolino, MD[4,5]

[1]Dermatology and Venereology, Department of Internal Medicine, "Celio" Military Hospital of Rome

[2] Department of Oncology, "Celio" Military Hospital of Rome

[3] Service of Surgical Pathology, "Celio" Military Hospital of Rome

[4]Unit of Dermatology, IRCCS University Vita-Salute San Raffaele, Milan, 20132, Italy

[5] Department of Dermatology, Dipartimento di Medicina Interna e Specialità Mediche, La Sapienza University of Rome, Italy;

Corresponding Author: Giovanni Paolino

Tel: 0039-349-8465167

FAX: 0039 0981 58179

Email: paolgio@libero.it

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Lentigo maligna(LM)is an *in situ* form of cutaneous melanoma that commonly arises on the head and neck in elderly patients.The main challenge of LM is its highest rate of local recurrence(Fosko et al.,2018).In this regard, Mohs surgery has consistently demonstrated lower recurrence rates of 0.3% to 2.2%(Kunishige et al.,2012; Moyer JS, et.al,2017).However,despite this, its treatment remains difficult.Indeed, the head and neck region, for anatomic purposes, are typically associated with higher recurrences and/or aesthetic impairment(Fosko SW et al.,2018).Finally, the age is a further factor, since elderly patients with LM may have several comorbidities, which could be important contraindications for the surgery.

Imiquimod 5% cream is increasingly applied in the treatment of LM for inoperable patients and in particular for large lesions where surgery may lead to disfiguring scars.We report two cases of inoperable LM, successfully treated with imiquimod 5% in occlusion(Fig.1a-f).

A 83-year old Caucasian female patient, presented to our Department with an atypical pigmented lesion of the nasal pyramid.Her personal medical history was positive for ischaemic cardiopathy, type II diabetes, arterial hypertension, allergic diathesis and past adverse anaphylactic reaction to local anesthetics. The second case consisted in a 85-year old Caucasian female patient, that presented to our Department for an atypical pigmented lesion in the right zygomatic area. Her personal medical history was positive for ischaemic cardiopathy and installation of a pace-maker.Both patients performed an incisional biopsy and were reluctant to perform surgical excision, also due to their comorbidities. In both cases the histological examinations confirmed the diagnosis of LM.

In order to improve the therapeutic response(with the informed consent of the patients and after the evaluation of the local ethics committee), we arbitrarily decided to treat our patients with imiquimod 5% cream, following the scheme:1 dose 2 times a day(12.5 mg in 250 mg cream during the morning and in occlusion during the evening 12h/24)for 5 days a week, at alternate week, for 5 weeks(3 of treatment and 2 of stop), for a total of 30 doses, 15 of which applied in the evening in occlusion (12h/24).(Fig.2)During the treatment no systemic adverse outcomes were recorded, except a mild fever in the first case(37.2 C°),which arose in 19th-21st days.

As local side effects, itching, crusting and mild burning were reported at the end of each week of treatment, with a relative disappearance during the week of pause.Both patients referred to tolerate better the drug administration rather than undergo surgery.Clinical follow-up was performed with dermoscopic examination, sonography control of the regional nodes, seric evaluation of lactic dehydrogenases(LDH) and S100, specifically after one month of therapy and successively every six months.Both patients did not show local and/or systemic recurrences after 36 and 24 months of follow-up, respectively.

The use of imiquimod for LM was first described in 2000,and subsequently numerous studies have highlighted a range of benefits and limitations(Ahmed et al.,2000). However, up to date, there is not a standardized use of imiquimod 5% for LM, accordingly there is the need for a consensus through a prospective, randomized controlled trial with long-term follow-up.

Previous retrospective studies have documented a clinical response rate of 73% after a 40-month follow-up(Fosko et al.,2018), while a systematic review of mainly retrospective studies showed a 77% histological clearance rate(Tio D et al.,2010).

Specifically, the better response to imiquimod 5% was present in patients that developed an intense cutaneous reaction with an intense inflammation(Tio et al.,2010).This is due to the mechanism of action of the drug, that is a Toll-like receptors 7 and 8 agonist, which allows the release of Interferon-alfa,Tumor Necrosis Factor-alfa and Interleukin-6, increasing the local and systemic immune response.According to these features, we decided to use an occlusion for the treatment of our two patients.In this way, occlusion increases the absorption of the drug, by enhancing the penetration. Besides, considering that usually LM has a wide and subclinical extension, the treatment in occlusion may increase the probability to treat also the peripheral areas with underlying LM (not yet clinically visible) through the centrifugal physical expansion of the cream, pushed by the occlusive means.

In conclusion, for inoperable patients it is needed to propose alternative treatments, considering that LM may progress into an invasive melanoma in 2.2%-50% of cases.(Fosko et al.,2018)In this spectrum, imiquimod 5% cream in occlusion, may be a valid therapeutic alternative, although only palliative.(Cliff , 2016;De Luca et al.,2018)The need for standardization of treatment schedule and outcome measures remains a pivotal point.

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Figure legends

Figure 1: a) a 83-year old Caucasian female with a lentigo maligna (LM) of the nasal pyramid; *insert upper left:* asymmetric pigmented follicular openings, dark rhomboidal structures, slate gray dots; b) the lesion at the end of the treatment, with the typical local side effects due to imiquimod 5% cream; c) complete resolution and absence of recurrences after 36 months of follow-up; *insert upper left:* absence of dermoscopic alterations; d) a 85-year-old female patient with a LM of the right cheekbone; *insert lower left:* central hyperpigmentation, asymmetric pigmented follicular openings, slate grayish-blackish dots;e) typical local side effects of the treatment with, inflammation, crusts and erosions;f) complete resolution of the lesion, without recurrence after 24 months of follow-up. The whitish scar, is the sign of the biopsy; *insert lower right:* absence of dermoscopic features of LM and presence of only ectatic vessels.

Figure 2. The scheme reported above has been performed for a total of 5 weeks, of which 3 of treatment and 2 of stop.