Ingenol Mebutate 150 mg as Physician-Directed Treatment of Bowen’s Disease Under Occlusion

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Abstract
Ingenol mebutate (IM) is a topical pharmacotherapy approved in Switzerland since 2012 for treating non-hypertrrophic, non-hyperkeratotic actinic keratosis. We report a case with off-label use of IM where Bowen’s disease has been successfully treated with physician-directed IM 0.015% gel under occlusion over the chest area.

Case Report
We describe the case of a 82-year-old Caucasian man, Fitzpatrick skin type II, followed up at our clinic for a history of severe sun-damaged skin, actinic keratosis and multiple keratinocyte skin cancers.

The patient presented with 4 shiny red, well-demarcated plaques with/without scaling on the chest. Dermoscopy showed a clear pattern of dotted vessels. Based on the clinical and the dermatoscopical appearance of the lesions, a diagnosis of multiple Bowen’s disease was made (fig. 1).

Based on the patient’s preference for non-surgical treatment, we presented him with different topical treatment options. As the mobility of his hands was limited following orthopedic surgery, a physician-directed treatment was needed. Photodynamic therapy was declined by the patient on account of the expected pain associated with the procedure. Cryotherapy was deemed less suitable due to the number of lesions and potentially long wound healing. We decided to use IM as a physician-directed treatment, employing an occlusive dressing to enable a single application to elicit a thera-

Key Words
Ingenol mebutate · Bowen’s disease · Photodynamic therapy

Introduction
Bowen’s disease is an in-situ squamous cell carcinoma of the skin with approximately 3–5% of risk of progression to invasive carcinoma [1]. Although surgical excision is the definitive treatment, non-surgical treatment modalities including photodynamic therapy, 5-fluorouracil and imiquimod are effective alternatives for Bowen’s disease, especially in patients who are poor candidates for surgery [2]. Judging by clinical experience, Bowen’s disease is harder to treat than actinic keratosis. We herein report a case of Bowen’s disease successfully treated with physician-directed ingenol mebutate (IM) 0.015% gel under occlusion over the chest area.
As we expected an increased local skin reaction due to occlusive application, we chose the lower of the 2 concentrations of IM available for this off-label treatment. We directly applied 150 μg IM gel on each lesion with a surface area of around 2 × 2 cm to extend 5 mm beyond the lesion. The treatment area was then covered with a waterproof bandage for 1 day to assess the local skin response under occlusion. At the same time, we used cryotherapy on one circumscribed, clinically diagnosed non-hypertrophic actinic keratosis over the right temporal area. Starting on the third day, the patient experienced erythema extending beyond the application site, pain within the area of application, which he reported as similar to what he perceived in the right temporal area treated with cryotherapy. The local skin reaction on the chest lasted almost 2 weeks. No systemic symptoms such as fever, chills, fatigue or malaise were reported. At 3-month follow-up, we repeated the treatment at our office on the 4 lesions of BD. This time, we asked the patient to keep the bandage on for 2 days because the lesions had persisted. At 6-month follow-up, 2 lesions of Bowen’s disease went into clinical remission (fig. 2). Two lesions of BD persisted and were again treated as described above for 2 days under occlusion (fig. 2).

**Discussion**

In Switzerland, registered non-surgical treatments for BD include topical 5-fluorouracil, photodynamic therapy and cryotherapy. Topical 5-fluorouracil 5% cream clinically cured 85% of patients in one small, uncontrolled study, administered twice daily for an average of 8 weeks (average follow-up time = 4.6 years) [3]. The efficacy of PDT for Bowen’s disease was illustrated by a randomized trial in which 225 patients were randomly assigned to PDT with MAL (MAL-PDT), PDT using a placebo or conventional treatment (either cryotherapy or topical 5-FU). The lesion recurrence rates at 12 months were similar with MAL-PDT, cryotherapy and topical 5-FU (15, 21 and 17%, respectively) [4]. Cryotherapy appears to have a good success rate for Bowen’s disease with adequate treatment (recurrences less than 10% at 12 months) but healing may be slow for broad lesions and discomfort may limit treatment of multiple lesions. Curettage and PDT both have higher success rates and less discomfort overall, but are more time-consuming and/or expensive to perform [5]. A systematic review of observational studies that identified 8 studies (with a total of 273 patients) that assessed recurrence rates for invasive cutaneous SCC after cryotherapy found a pooled average recurrence rate of 0.8% (95% CI 0.1–2.2) [6].

Frequently used as off-label treatment for BD in Switzerland, imiquimod cured BD at a rate between 73 and 88% in one small, randomized trial and several small, uncontrolled studies [7].

IM is a topical drug extract from the latex sap of a plant *Euphorbia peplus* that acts by chemo-ablative and immune-stimulatory properties [8]. Its dual mechanism of action consists of a rapid induction of inflammation with primary necrosis of tumor cells, followed by neutrophil-mediated, antibody-dependent cellular cytotoxicity of residual cells [9]. The Food and Drug Administration ap-
One case report from South Korea and one from Germany describe successful treatment of Bowen’s disease outside the facial area with IM 0.05%. The South Korean report had used IM 0.05% once daily for 3 days consecutively on one lesion over the right calf. Ten weeks after treatment, clinical remission was confirmed histologically by multiple punch biopsies without evidence of BD [11]. The German case used IM 0.05% once daily for 2 days consecutively on 2 lesions. At 2-month follow-up, one lesion was clinically resolved confirmed by punch biopsy, while the second lesion needed retreatment [12]. Intra-epidermal carcinomas were clinically healed in 94% of patients in a clinical study employing Euphorbia peplus sap with IM (previously labeled as PEP005) [13].

Our case report adds to the data on treatment of BD using IM. Our treatment protocol with a single application at the time of consultation in our clinic allowed using IM as a one-time intervention akin to PDT. In contrast to PDT, our treatment with IM was rapid and without immediate pain. The use of an occlusive dressing, although officially not recommended, may be a benefit when turning IM from a self-directed into a physician-directed treatment, addressing the needs of an elderly population and of anatomical sites difficult to access in self-directed treatment.

Statement of Ethics
Patient consent was obtained.

Disclosure Statement
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References