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COMMENTARY

Are topical beta-blockers really effective "in real life" for targeted therapy-induced paronychia

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Abstract

Paronychia and periungual pyogenic granuloma represent one of the most common and bothersome dermatologic toxicities observed with ErbB inhibitors. There is no standardized treatment, and management remains challenging. Moreover, conservative management with noninvasive treatment should be promoted for fragile patients in a metastatic setting. Over the last few years, the efficacy of topical blocking agents has been considered for managing cutaneous or mucosal pyogenic granulomas. Very recently, the use of topical propranolol or of timolol has been reported in several patients undergoing treatment with EGFR inhibitors and developing pyogenic granulomas of the nail. We performed a retrospective single-center review of patients with targeted therapy-related paronychia/periungual pyogenic granulomas who had been treated with topical timolol, either alone or in combination with other topical treatments. Nearly two thirds of patients showed at least a partial response after 1 month of therapy, and the use of a topical beta-blocker in our population was associated with a favorable safety profile. Finally, topical timolol may represent a promising treatment option for the management of cancer patients suffering from painful periungual lesions. Comparative clinical trials, however, are still needed.

Keywords Paronychia · Pyogenic granuloma · Timolol · Beta blocker · EGFR · Nail

Paronychia and pyogenic granulomas (PG) of the nail represent one of the most common and bothersome dermatologic toxicities observed with EGFR or pan-ErbB inhibitors [1, 2], and to a lesser degree with MEK or mTOR inhibitors [3]. They develop gradually over several weeks or months of treatment [1, 2], and affect approximately 20% of patients treated [4]. These vascular lesions result from the piercing of perionychium after thinning of the periungual stratum corneum [1], with an aberrant healing process. Lesions first manifest as acute paronychia (painful erythematous inflammation of the lateral nail folds), which can progress into the formation of friable granulation tissue (pyogenic granuloma) [1, 2]. Management for targeted therapy-induced paronychia remains very challenging [1]. Because lesions can be functionally debilitating, impair patients' quality of life and recur throughout the course of treatment, conservative management with noninvasive treatment should be promoted for fragile patients in a metastatic setting.

The non-cardioselective oral beta-blocker propranolol now represents the first line treatment for severe infantile hemangiomas [5]. It is hypothesized that this β-adrenergic receptor antagonist acts by inhibiting proangiogenic factors, by inducing peripheral vasoconstriction and by promoting apoptosis of proliferating endothelial cells. Similarly, the variable expression of beta-adrenergic receptors on the surface of a variety of vascular lesions has been recently demonstrated [6], including pyogenic granuloma. Consequently, the efficacy of topical blocking agents has been considered for treating all forms of PG, in both children and adults [7–12]. Overall, the therapeutic response with topical propranolol or timolol appears to vary, i.e., efficacy in cutaneous or mucosal PG may not be universal as in the case of infantile hemangiomas [7–12]. More recently, 1% topical propranolol cream was evaluated in a population of ten patients with PGs of the nail, including three with lesions induced by targeted therapies. Clinical responses to topical beta-blockers were conflicting, with a

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complete cure reported for fingernail PGs (three patients) whereas toenail PGs (nine patients) either did not improve or even worsened [13]. Authors speculated that the vehicle cream did not allow for adequate penetration into toenail lesions. Conversely, Cubiró et al. conducted a prospective open study in a population of nine patients developing paronychia/PGs induced by EGFR inhibitors [14]. They reported a complete clearance of toenail and fingernail paronychia and/or periungual PGs with topical timolol (0.5% gel, twice a day under occlusion for 1 month) in all patients except one. Moreover, topical beta-adrenergic receptor therapy proved to be safe and well-tolerated in this cohort.

We performed a retrospective review of patients with targeted therapy-related paronychia/periungual PGs who had been treated for at least 1 month with topical timolol (0.5% gel, twice a day under occlusion) in our academic oncodermatology department (Institut Universitaire du Cancer, Toulouse Oncopole). A majority of patients was treated with monotherapy, apart from five patients with persistent lesions after treatment with a combination of topical corticosteroids and antiseptics (two patients) or antiseptics alone and for whom these treatments were maintained. Patients were evaluated following similar clinical/photographic criteria as have been previously used [14], and were classified as complete response (CR, clearance of the lesion, absence of pain and/or bleeding), partial response (PR-improvement in at least one of the three items) or no response (NR). Thirteen patients were analyzed, including eight women and five men (age ranging from 37 to 80 years). All patients were treated with ErbB inhibitors, either with monoclonal antibodies or tyrosine kinase inhibitors (four patients with lapatinib, four patients with afatinib, three patients with cetuximab, two patients with erlotinib). After 1 month of treatment, no local or systemic adverse events were reported in any patient. Anticancer treatment was maintained in all cases. Fifteen percent of patients were considered in CR (2/13) (Fig. 1a–c), 46% in PR (6/13) and 39% in failure (5/13). It should be noted that clinical response was similar between patients suffering from both finger- and toenail PGs (seven patients) and those with exclusive toenail (five patients: three PR, one CR, one NR) or fingernail (one patient; NR) involvement. Likewise, no difference was observed among patients who developed paronychia (three patients)/PGs alone (six patients), or both (four patients), as well as between patients treated with monotherapy or in combination.

Overall, a significantly lower rate of complete response was achieved in our population, in comparison with that published by Cubiró et al. [14]. The latter results, obtained in a selected cohort of patients, might be possibly mitigated. However, nearly two thirds of our patients treated in "real life" showed at least a partial response after 1 month with topical β-blockers prescribed in monotherapy or in combination with topical corticosteroids or antiseptics. Furthermore, the use of topical timolol in our population was also associated with a favorable safety profile.

Although various treatment options have been proposed for targeted therapy-related paronychia/periungual PG, no randomized controlled studies have been performed, and there is no standardized or even first-line treatment [1, 2, 15, 16]. Recommendations are based on expert opinion and mainly include patient education with preventive measures (correction of nail curvature with braces or taping with stretchable tapes, avoidance of repeated friction and trauma/excessive pressure, trimming of the nails regularly, etc.), liquid nitrogen

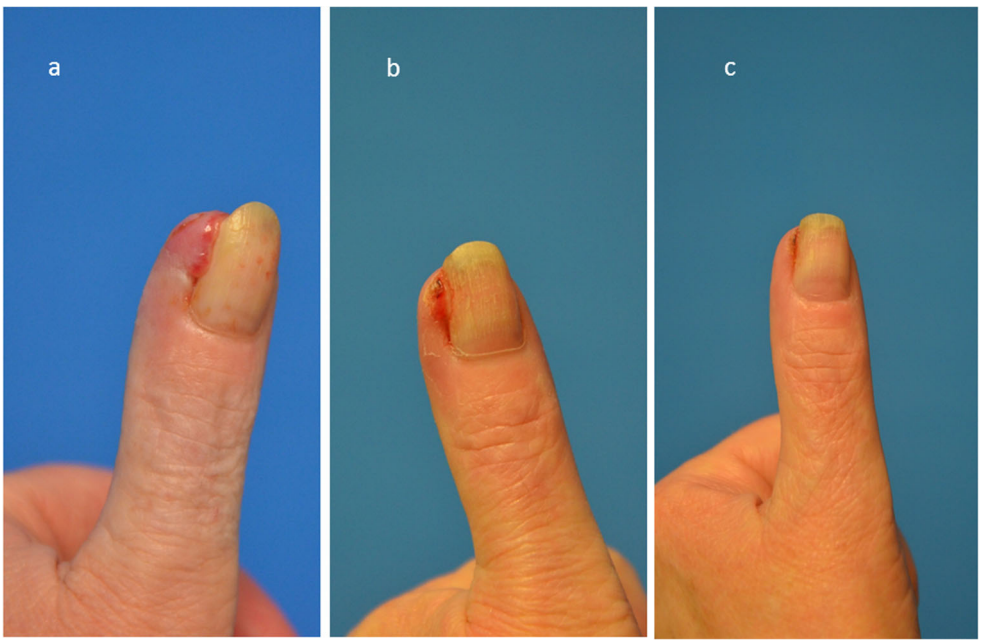

Fig. 1 **a**–**c** Progressive improvement after 2 weeks (**a**, **b**); complete healing after 1-month therapy with timolol gel (**c**)

or silver nitrate chemical cauterization, topical or oral antibiotics (in case of secondary superinfection), topical povidone iodine 2%, high-potency topical corticosteroids, or surgical treatment for refractory lesions (with partial nail plate avulsion and physical destruction of excessive granulation tissue) [1, 2, 15–18]. Management with a topical β-blocker is now emerging, and may represent a promising treatment option. It may obviate recurrent surgical excisions or aggressive treatments in fragile patients with cancer, and may improve a patient's quality of life, in limiting the functional impairment associated with paronychia and/or chronic PG. However, comparative randomized trials (versus best supportive care) with various lengths of treatment and different vehicles together with a prolonged follow-up are needed, which would make it possible to more accurately establish indications for routine use of topical β-blockers for periungual PGs in cancer patients.

Compliance with ethical standards

Conflict of interest Dr. Sibaud reports grants from Roche, grants from Novartis, grants from BMS, grants from Bayer, grants from Pierre Fabre, and outside the submitted work. Dr. Casassa has nothing to disclose. Mirella D'Andrea has nothing to disclose.

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