Ingenol Mebutate Treatment in a Patient with Gorlin Syndrome

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Ingenol mebutate can be used to treat (superficial) BCCs in patients with Gorlin–Goltz syndrome as an additional modality. Close clinical follow-up is recommended.

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Introduction

Gorlin syndrome, also known as the basal cell nevus syndrome (OMIM #109400), is a rare autosomal-dominant genetic disease. The characteristic multiorgan abnormalities are caused by mutations of the patched receptor gene (PTCH1), a tumor suppressor gene, on chromosome arm 9q. PTCH1 inhibits signaling by the membrane protein Smoothened (SMO). The loss-of-function mutation of PTCH1 results in an elevated activation of the sonic hedgehog pathway, which activates transcription factors such as GLI1. GLI1 induces cell cycle progression and cell proliferation and is associated in development of basal cell carcinoma (BCC) and medulloblastoma. Up to 40% of the patients show a de-novo mutation with negative family history. The prevalence is 1:60,000 with an equal frequency in women and men [1, 2].

Most patients develop multiple BCCs already in adolescence, which should raise the suspicion of Gorlin–Goltz syndrome. The BCCs are usually located on the face and trunk, but also occur on sun-protected areas. All histological subtypes from superficial to infiltrative and morphoeic BCC can be found. Aggressive forms such as the locally destroying ulcer terebrans are very rare. Other...
clinical features include mandibular keratocysts, palmar and plantar pits, skeletal abnormalities and malformations in the central nervous system and genital tract. Gorlin–Goltz patients need multidisciplinary medical care and follow-up as well as genetic counseling if the patients want to have children [3].

The treatment of multiple BCCs includes conventional surgery, micrographic Mohs surgery, cryotherapy, laser ablation, curettage and electrodessication, photodynamic therapy, imiquimod 5% cream, 5-fluorouracil cream as well as the sonic hedgehog pathway inhibitor vismodegib. Radiotherapy is contraindicated, since further BCCs could be induced, where the mutation of the PTCH1 gene causes an increased sensitivity to radiation [4, 5].

Ingenol mebutate is approved as a topical treatment of actinic keratosis. It is believed that the local effect inhibits the growth of cancer cells and/or induces tumor cell death. The incidence of local skin reactions is high, and it has proven to be safe and efficacious. Successful off-label treatment of superficial BCCs with ingenol mebutate has previously been shown [6].

Case Report

A 30-year-old Caucasian woman was diagnosed with Gorlin–Goltz syndrome in 2003, when multiple BCCs were detected. The diagnosis was based on clinical features such as palmar pits, hypertelorism, increased head circumference, calcification of the falx cerebri, multiple ovarian cysts and fibromas and the radiologic evidence of odontogenic keratocysts. Genotyping of the PTCH1 gene detected a heterozygous mutation. Over 10 years, the patient was treated with numerous procedures such as micrographic Mohs surgery, conventional surgery, photodynamic therapy and topical therapy with imiquimod cream. In 2014, we initiated a systemic therapy with vismodegib, which showed a pronounced response with decrease of most of the BCC. The patient developed alopecia, dysgeusia and pronounced long-lasting fatigue. Eventually, the patient decided to stop vismodegib therapy after 6 months on account of side effects impairing her quality of life. BCC recurred after 3 months but the patient was tired of surgery and asked for an alternative therapy. Cryosurgery was very painful and also resulted in extensive scarring. We treated multiple BCCs on her back with 500 μg/g of ingenol mebutate gel (fig. 1). Her husband applied the gel for 2 consecutive days. She reported a local inflammatory reaction, which healed after 2 weeks. Clinically, the treated BCCs showed complete resolution without scarring (fig. 2). The patient repeated the treatment on a regular basis without affecting her daily life and work. During the follow-up over 8 months, no recurrence of the treated BCC was detected. Of course, occasional surgery of more invasive BCCs was not completely unavoidable but the patient was happy to be able to treat many BCCs on her own without a great effort and side effects.

Conclusion

Ingenol mebutate seems a suitable off-label option to treat (superficial) BCCs in patients with Gorlin syndrome. The treatment is easy to manage and patients appreciate being able to treat autonomously.
Informed consent for image acquisition, biopsy specimen sampling and treatment (including evidence-based and off-label use) was obtained from the patient.

References


Statement of Ethics

The authors declare no conflicts of interest.

Disclosure Statement