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Clinical and molecular effects of HeberFERON in patients with multiple basal cell carcinoma

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Letter to editor

The development of multiple basal cell carcinoma (mBCC) in a single non-syndromic, immunocompetent individual is relatively common. Patients are generally classified as having mBCC when more than one lesion is present; however, contemporary literature frequently defines mBCC as the occurrence of more than three lesions.[1]

Several hereditary syndromes are associated with the development of mBCC, most notably Gorlin–Goltz syndrome (GGS). This autosomal dominant disorder is characterized by a marked predisposition to multiple BCC, as well as palmoplantar pits and odontogenic keratocysts of the jaws. Clinical manifestations typically arise during childhood or adolescence. GGS results from germline mutations in the PTCH tumor suppressor gene located on chromosome 9 (9q22.3–q31), leading to constitutive activation of the Hedgehog (HH) signaling pathway.[2]

Non-surgical therapeutic strategies are generally preferred in patients with mBCC. However, in individuals with GGS, no consensus exists regarding an optimal standard of care. Given the high mutational burden characteristic of these patients, HH pathway inhibitors have been proposed as a treatment option for mBCC; nevertheless, their long-term efficacy and safety profiles remain to be fully established.[3,4]

Among the agents evaluated over recent decades for the treatment of BCC are interferons (IFNs), a family of cytokines with well-established immunomodulatory and antineoplastic properties.[5]

HeberFERON is a co-formulation of interferon alfa-2b and interferon gamma that exhibits antiproliferative, antiangiogenic, and immunomodulatory effects.[5]

We report three cases with mBCC treated with HeberFERON. Before and after treatment each patient had a sample of healthy skin and of the BCC 3 mm punch for histopathological and molecular study. The first case was a 68-year-old immunocompetent female agricultural worker presented with four facial lesions. The largest lesion measured 20 mm in diameter and was ulcerated, with a tendency to bleed easily. Histopathological examination confirmed solid-type BCC.

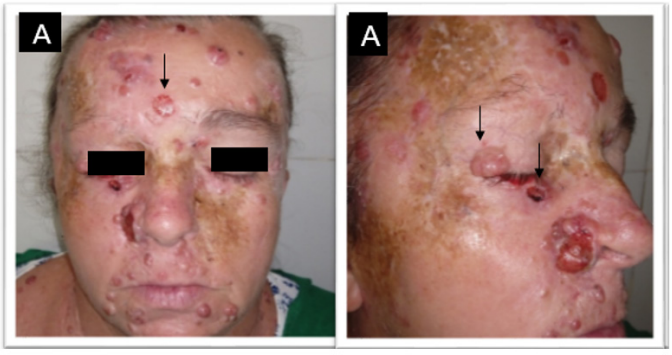
The second case was a 75-year-old immunocompetent male agricultural worker presented with four ulcerated and crusted lesions located on the anterior thorax. The largest lesion measured 30 mm in diameter. Histopathology revealed superficial BCC.

The third case was a 41-year-old female reported multiple cutaneous tumors since the age of 20 years. Lesions were variable in size, round, elevated, well-demarcated, plaque-like, and pigmented. They were too numerous to count and were distributed over the face, neck, back, upper limbs, and anterior thorax. Physical examination revealed palmar pits and frontal bossing. Biopsies obtained from four representative lesions confirmed BCC of various histological subtypes, including solid, superficial, and adenoid variants.

Patients were evaluated by dermatology and oncology specialists. Radiological imaging and laboratory investigations were performed, and patients were followed for one year. Clinical response was assessed according to RECIST version 1.1 criteria: complete response (CR), defined as total disappearance of the lesion; partial response (PR), defined as at least a 30% reduction in the sum of the longest diameters; and stable disease (SD).[6]

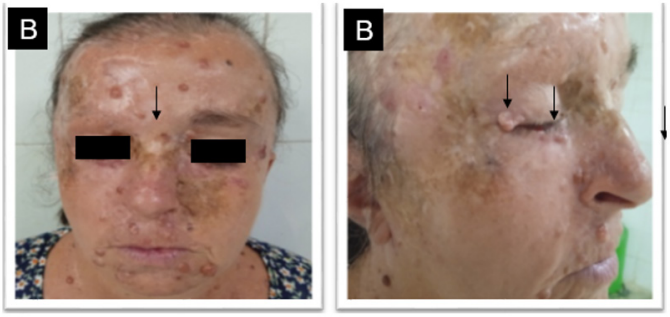
HeberFERON (10.5×10^6 IU) was administered perilesional and intradermal three times weekly for three weeks in an outpatient setting. Two patients achieved a complete response, and one achieved a partial response in the treated lesion. Additional tumors adjacent to the treated lesions were monitored and demonstrated complete or partial responses (Figure 1). Adverse events, most commonly transient fever, were frequent but mild and did not require treatment discontinuation.

Figure 1A) Gorlin Syndrome. Initial evaluation. The ulcerate lesion of the



right nasal wing was infiltrate with HeberFERON. The lesion indicated by the black arrow were evaluated at the end of treatment.

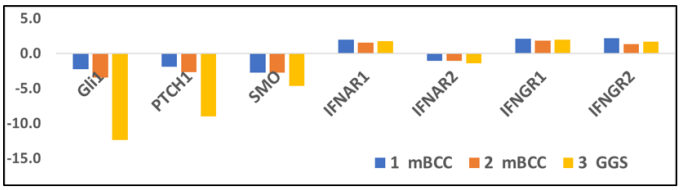
Figure 1B) Gorlin Syndrome after one year of the treatment.



Molecular analyses were performed on tumor tissue and adjacent healthy skin samples obtained before and after treatment. Samples were lysed, and total RNA was extracted using the RNeasy Plus Mini Kit (Qiagen). Complementary DNA (cDNA) was synthesized, and quantitative polymerase chain reaction (qPCR) was performed to evaluate relative gene expression of HH pathway components (PTCH1, SMO, and GLI1) and interferon receptor chains (IFNAR1/2 and IFNGR1/2).[7]

Post-treatment analysis demonstrated increased expression of IFNAR1, IFNGR1, and IFNGR2, confirming activation of interferon signaling pathways. Conversely, expression levels of GLI1, PTCH1, and SMO were consistently reduced across all three cases. These findings suggest that HeberFERON exerts its therapeutic effect in mBCC, at least in part, through modulation of the Hedgehog signaling pathway (Figure 2).

Figure 2 Changes in gene expression in healthy skin following treatment,



showing expression of Hedgehog pathway genes (GLI1, PTCH1, and SMO) and interferon receptor genes (IFNAR1/2 and IFNGR1/2) in the three cases (non-syndromic mBCC and Gorlin–Goltz syndrome).

BCC is the most prevalent keratinocyte-derived malignancy in humans. Ultraviolet (UV) radiation remains the principal etiopathogenic risk factor. The occurrence of multiple BCCs in a single non-syndromic, immunocompetent individual is common. Although definitive predisposing factors have not been fully characterized, the presence of multiple lesions at the time of initial dermatologic evaluation has been identified as a strong predictor of subsequent tumor multiplicity.[8]

Genetic studies have demonstrated that inherited and somatic mutations affecting components of the HH signaling pathway play a central role in BCC pathogenesis. Approximately 75% of BCCs harbor mutations in the PTCH1 gene, while mutations in SMO are detected in approximately 20% of cases. These molecular alterations lead to aberrant pathway activation, promoting tumor proliferation and survival.[9]

Non-surgical treatment strategies are frequently preferred in patients with multiple BCCs (mBCC), including those with Gorlin–Goltz syndrome (GGS), as lesions are commonly located in the facial region, where repeated surgical procedures may result in extensive scarring and negatively affect quality of life. Although surgery remains the first-line treatment according to current guidelines, it may not permit complete tumor clearance in patients with numerous or subclinical lesions. Moreover, many tumors arise in high-risk anatomical areas where topical therapies such as imiquimod and 5-fluorouracil cannot be safely used due to an increased risk of recurrence. Under these circumstances, alternative therapeutic approaches are required.[5,10]

HeberFERON may represent a valuable therapeutic option for this group of patients. The antitumor activity of interferons (IFNs) is mediated through inhibition of tumor cell proliferation and induction of apoptosis. The combination of two interferons provides enhanced and prolonged pharmacological activity without increased toxicity, resulting in a faster onset and more sustained therapeutic response compared with interferon monotherapy.[10] These properties support its potential role in the management of mBCC, particularly in patients for whom conventional treatments are limited.

HeberFERON may represent a therapeutic option for patients with mBCC, potentially exerting its effects through modulation of the HH signaling pathway, a key molecular mechanism involved in tumor proliferation and progression.

Acknowledgment

None.

Ethical approval

The Institutional Ethical Board of Polyclinic Juana Naranjo Leon approved the protocol for this study. All participants gave their written informed consent. The procedures and data management were in accordance with Good Clinical Practice guidelines and the ethical principles stated in the Declaration of Helsinki.

Ethic statement

The patients in this manuscript have given written informed consent to publication of their case details.

Conflict of interest

The authors declare there is no conflict of interest.

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