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REVIEW

Profile of vismodegib and its potential in the treatment of advanced basal cell carcinoma

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Abstract: Basal cell carcinoma (BCC) is the most common human malignancy. Recent advances in our understanding of the critical biologic pathways implicated in the development and progression of BCC have led to the development of the first molecular targeted therapy for this disease. The hedgehog pathway is mutated in virtually all patients with BCC and recent trials with vismodegib, an inhibitor of this pathway, have shown significant responses. This review will discuss the importance of the hedgehog pathway in the pathogenesis of BCC and describe in detail the pharmacology of vismodegib in relation to its activity in advanced BCC.

Keywords: basal cell carcinoma, vismodegib, hedgehog pathway

Introduction

Basal cell carcinoma (BCC) is the most common human malignancy. Since it is not always included in cancer registries, the true incidence is unknown. It is estimated that approximately 3.5 million nonmelanoma skin cancers in 2.2 million patients are treated annually in the United States, the majority of which are BCC (American Cancer Society, Facts and Figures 2013). The American Academy of Dermatology estimates that approximately 2 million BCC are treated every year (http://www.aad.org/dermatology-a-to-z/diseases-and-treatments/a---d/basal-cell-carcinoma). Fortunately, these tumors are usually amenable to local therapy and only 1%–5.3% of lesions recur after initial resection.[1]

Interestingly, even locally aggressive tumors seldom metastasize and metastatic BCC is quite rare. Since accurate incidence records of this disease are not available, the burden of metastatic disease is difficult to ascertain. Rates ranging from 0.0028% to 0.55% of patients with BCC developing metastases have been reported,[2–7] but even these have been questioned.[8] The median age of patients with metastatic BCC at the time of diagnosis of the primary lesion is about 45–56 years, and metastases appear at a median of about 9 years later.[9–11] Factors that may predispose to the development of metastatic BCC include male gender,[9] primary lesion in the ear region[9,11,12] and face,[11] large[11] and locally invasive[13] primary tumors, recurrence following initial treatment,[11] and impairment of cell mediated immunity (eg, acquired immunodeficiency syndrome, therapeutic immunosuppression).[14,15]

Recent advances in our understanding of the biologic pathways that appear to be important in the development and progression of BCC have led to the development of the first molecular targeted therapy for this disease, vismodegib. The hedgehog (Hh) pathway is mutated in virtually all patients with BCC and inhibition of this pathway with vismodegib appears to result in significant clinical responses. The following

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