QUESTIONS
1. A 23-year-old man presents with a 1.1-cm lesion (see image above) that arose a few months ago on the central forehead. What would be the next step in management?
   a. Surgical excision.
   b. Cryosurgery.
   c. Topical chemotherapy.
   d. Mohs micrographic surgery (MMS).
   e. Electrodissection and curettage (ED&C).

2. A year after the appropriate care was administered, the patient developed a 3-cm lesion on the back of his thigh. Histopathologic examination of the lesion showed basal cell carcinoma (BCC), sclerosing type, with perineural invasion and positive margins. The patient refuses surgery. An appropriate evaluation and genetic testing confirmed that the patient has basal cell nevus syndrome. Which of the following therapies would be most appropriate in this case?
   a. Topical chemotherapy.
   b. Cryosurgery.
   c. Vismodegib.
   d. Electrodissection and curettage (ED&C).
   e. Radiation.

3. The patient did not respond to treatment. The hedgehog (Hh) pathway and other potential targeted genes associated with BCC tumor development are being studied to further elucidate the cases of resistance against Hh-inhibiting agents. Which of the following group of cells has been proposed as a target of gene therapy to regulate the formation of BCC?
   a. Bulge hair follicle stem cells.
   b. Bone marrow–derived stem cells.
   c. Multipotent stem cells in follicles and the interfollicular epidermis.
   d. $CD4^+ CD49f^{high} CD34^{intermediate} Sca1^+$ cell population in the skin.
ANSWERS

1. **d.** Mohs micrographic surgery (MMS).

   Basal cell carcinoma (BCC) is the most frequently encountered skin cancer. Treatment guidelines must be personalized and vary according to size and location of the lesion, pathological features, recurrence, and other factors (Connolly *et al.*, 2012; U.S. Preventive Services Task Force, 2009). MMS (choice d) appropriate-use criteria include (i) lesions $\geq 6$ mm in diameter located in the central face, mandible, temple, pre- and postauricular areas, ears, hands, and feet; (ii) lesions $>10$ mm located in the head and neck, different from the locations mentioned above; (iii) lesions $>20$ mm in all other areas; (iv) aggressive histology (morpheaform, sclerosing, or mixed infiltrative); (v) recurrent lesions; (vi) lesions located at sites of prior radiation; (vii) lesions with poorly defined borders; (viii) immunocompromised patients; and/or (ix) lesions with perineural invasion.

   Cryosurgery (choice b), topical chemotherapy (5-fluorouracil or imiquimod) (choice c), and ED&C (choice e) are not recommended for treatment of high-risk BCC.

2. **c.** Vismodegib.

   It has been demonstrated that 90% of sporadic BCC and those in patients with basal cell nevus syndrome (BCNS) have *Ptch* mutations (Uhmann *et al.*, 2014). PTCH1 receptor is normally a negative regulator of the Sonic Hedgehog (Hh) signaling pathway (Adolphe *et al.*, 2006). When mutated, it is no longer able to regulate smoothened (SMO) and leads to uninhibited activation of downstream targets, including Gli1 protein, which results in the production of several growth factors, favoring tumor initiation and progression.

   In January 2012, the US Food and Drug Administration approved vismodegib, an SMO inhibitor, for the treatment of metastatic or recurrent locally advanced BCC in patients who cannot undergo surgery or radiation (LoRusso *et al.*, 2011; Meiss and Zeiser, 2014). However, this drug is not curative and there have been reports of cases unresponsive to vismodegib, as well as studies in mice in which BCC-initiating cells were resistant to Hh-inhibiting agents (Kim *et al.*, 2014; Colmont *et al.*, 2013). Although mutations to the Hh pathway are associated with BCC initiation, it has been hypothesized that there is a need for a multihit process for the cells to obtain tumorigenic characteristics. Several investigators have supported this theory in the past (Colmont *et al.*, 2013; Uhmann *et al.*, 2014; Villani *et al.*, 2010), and it is now supported by Uhmann *et al.* (2014), who were able to demonstrate
that \( \text{Ptch}^{\text{flox/flox}} CD4^{\text{Cre}^{+/-}} \) mice can develop BCC only after treatment with DMBA/TPA (7,12-dimethylbenz(a)anthracene and 12-\(O\)-tetradecanoylphorbol-13-acetate).

Topical chemotherapy (choice a), cryosurgery (choice b), and ED&C (choice d) are not adequate treatment options in this case, given the tumor size and characteristics. Radiation (choice e) is not adequate either, because it may increase tumor size in patients with BCNS.

3. e. All of the above.

It is hypothesized that BCC is derived from multipotent stem cells located in the hair follicle bulge, cell reservoir in follicles, or the interfollicular epidermis. Some investigators have suggested that BCC can also develop from bone marrow cells because they can integrate into the epidermis and hair follicles (Uhlenmann et al., 2014).

Uhlenmann et al. (2014) performed several experiments to trace the BCC initiating cells and found that these were CD4\(^+\), \(\text{Ptch}\)-deficient cells. However, these were not stem cells from the bulge of the hair follicle, epidermal T cells, bone marrow, or any other previously described cell population that could give rise to BCC. Interestingly, BCC in this mouse model originated from \(\text{Ptch}\)-deficient, CD4\(^{\text{Cre}}\)-expressing epidermal cells. Furthermore, this cell population is CD4\(^+\)CD49\(^{\text{high}}\)CD34\(^{\text{intermediate}}\)Sca1\(^+\); none of the other stem-cell populations has this marker profile.

REFERENCES


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