Multiple Nodular Basal Cell Carcinomas Successfully Treated with Vismodegib: A Case Report and Discussion

Objectives:

- Review Basal Cell Carcinoma.
- Discuss indications for nonsurgical modalities for Basal Cell Carcinoma, with emphasis on Vismodegib.
- Review mechanism of action of Vismodegib.
- Review side effects of Vismodegib.
- Discuss management of side effects, as well as administration protocols of Vismodegib.
Introduction:

- Basal Cell Carcinoma (BCC), a malignant growth of basal cells of the epidermis, is the most common malignancy of the skin.
- The incidence and mortality of BCC is increasing worldwide, with more than 2.8 million new cases diagnosed and over 3,000 deaths yearly. This is incredibly pertinent to the healthcare system, as the cost of care for nonmelanoma skin cancers ranks fifth in the Medicare population with regards to cancer.

Introduction:

- The mainstay treatment for BCC includes excision and Mohs micrographic surgery.
- There exists a subset of patients with BCC that would benefit from non-surgical modalities for treatment.
  - This includes the elderly, immunocompromised, those with poor functional status, cosmetically sensitive areas, metastasis, and patient preference.
- Non-surgical treatment options include electrodessication and curettage (ED&C), cryosurgery, topical field therapy (Imiquimod or 5-fluorouracil), photodynamic therapy (PDT), lasers, and vismodegib.
Introduction:

- In 1997, novel research linked BCC with mutations in the hedgehog (Hh) signaling pathway.
- The Hh pathway is activated by the binding of hedgehog ligand to the protein patched homolog 1 (PTCH1) receptor. Once bound, it relieves the inhibition of smoothened (SMO), which activates the downstream glioma-associated oncogene homolog (Gli) family of transcription factors. The elimination of coordinated inhibition leads to aberrant constitutive activation of proto oncogenes and the development of BCC. The overexpression of mRNAs encrypting these above proteins are increased in BCC.

Introduction:

- In January 2012, the FDA approved the first oral medication for treatment of BCC, Vismodegib (Erivedge®), an inhibitor of the Hh pathway.
- A phase II, multicenter, international, two-cohort, nonrandomized study demonstrated high rates of tumor control in the indicated patient populations including a response rate of thirty percent (30%) in patients with metastatic BCC (mBCC) and forty-three percent (43%) in locally advanced BCC (laBCC).
- Indications for the use of Vismodegib in the United states, as defined by the National Comprehensive Cancer Network, are for the treatment of BCC not appropriate for surgery or radiation, such as cases that are metastatic or locally invasive.
Case Presentation:

- Our patient is a 64-year-old Caucasian male, referred to our dermatology clinic by the U.S. Department of Veterans Affairs for evaluation of a large non-healing lesion on the left lower back and concern for numerous clinical basal cell carcinomas.

- Initial dermatological examination revealed a 10mm pearly, pink papule on the right upper cheek, a 4.5 x 2.5cm ulcerated plaque on the left lower back, two additional approximately 1.0cm erythematous, scaly patches on the right upper back, a 2.5cm ulcerated plaque on the right chest, and a 2cm pink plaque on the left upper abdomen. The findings were consistent with various types of clinical BCCs.

Case Presentation:

- Three shave biopsies were obtained at the time of visit and revealed a nodulo-infiltrative BCC on the left lower back, a nodular BCC on the right chest, and a nodular BCC on the right upper cheek.

- Despite our recommendation the patient declined all surgical interventions. Due to the patient’s large tumor burden, the decision was made to proceed with a trial of Vismodegib. The patient was started on 150 mg Vismodegib once daily with monthly follow up. At four-month follow up, all ulcerated plaques had healed, and only small erythematous plaques remained. The patient noted a significant improvement in his quality of life following resolution of the ulcerated plaques. He was placed on a medication holiday at this time due to side effects.
Discussion:

• Despite a generally safe profile, the adverse effects of Vismodegib pose a clinical dilemma particularly with determining length of treatment. The decision to discontinue therapy is often due to intolerability of the side effect profile as it relates to quality of life.
  • The most commonly reported Vismodegib induced adverse effects include muscle spasms (70%), alopecia (60%), dysgeusia (55%), weight loss (45%), fatigue (40%), nausea (30%), diarrhea (30%), decreased appetite (25%), constipation (20%), arthralgias (15%), vomiting (12%), and ageusia (10%).
  • Management of these side effects are crucial to the successful use of vismodegib.

Discussion:

• Medication holidays, in addition to supportive care, have been used for the alleviation of VIAEs. To our knowledge, there is no established ideal length of time for a medication holiday from Vismodegib. However, a few studies have demonstrated that 3 week medication holidays in between treatment reduced adverse effects while maintain efficacy of treatment.
  • One study reported that medication holidays with a median duration of 22 days offered a decrease in VIAEs. Medication holidays are encouraged, as increased number of holidays was associated with longer duration of Vismodegib therapy without compromising efficacy.
  • An additional study reported that administering the medication in a 1 week on, 3 weeks off (maximum) was able to reduce side effects while still seeing resolution of the malignancy.
  • Limitations of these studies include sample size, and lack of biopsy proven results, but its all we have.

Discussion:

• With the information acquired from the previous studies, the following treatment protocol is proposed:
  • If choosing to stop vismodegib, other options for treatment of BCC must be discussed if clinically evident malignancy still present.

Vismodegib 150 mg daily  \[\rightarrow\]  Vismodegib 150 mg one week on, one week off  \[\rightarrow\]  Vismodegib 150 mg one week on, two week off  \[\rightarrow\]  Vismodegib 150 mg one week on, three week off  \[\rightarrow\]  Stop Vismodegib

\[X = \text{Intolerance of side effects despite management.}\]
Conclusion:

- To our knowledge, there is no thorough study that demonstrates the BEST protocol for administrating vismodegib.
- It is all based on the patients tolerance and response to the medication.
- You may consider treating the side effects with aforementioned modalities.
- You may consider a protocol of up to 3 weeks off, 1 week on in the case of severe adverse events.
- Further studies are needed for the ultimate length of treatment.

Thank you!
References