Hedgehog Signaling Inhibition in the Treatment of Basal Cell Carcinoma

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I. **Objectives:**
- Review the basics of the Hedgehog pathway
- History of the discovery of the PTCH-Smoothened complex
- Describe the genetics of Basal Cell Nevus Syndrome and its implications for sporadic basal cell carcinoma
- Review the studies leading to the FDA-approval of vismodegib and sonidegib: How good are they?
- What are the clinical indications for using smoothened inhibitors?
- Strategies for management of side effects: is there anything to be done?
- What are the other clinical scenarios where smoothened inhibitors may be beneficial?
- Future directions

II. **Origins of the PTCH-Smoothened cell surface proteins:**
- Hedgehog signaling pathway: Was discovered in Drosophila and found to be critical to embryogenesis. There are three types of Hedgehog proteins: DHh, IHh, and SHh. It is the sonic hedgehog protein (SHh) that is best known in vertebrates.
- **PTCH1** (protein patched homolog 1) is a transmembrane protein that inhibits a second transmembrane protein, Smoothened (SMO)
- When SHh is bound to **PTCH1**, **PTCH1** disinhibits SMO
- When SMO is uninhibited by **PTCH1**, it activates the cellular transcription factor **GLI 1** and **GLI 2** (named from “glioblastoma” from which they were isolated)
- The GLI transcription factor actions on the nucleus are implicated in 90% of basal cell carcinomas

III. **Basal Cell Nevus Syndrome:**
- Cause by a mutation in the **PTCH1** gene on chromosome 9q
- The syndrome was described by Robert J. Gorlin (1923-2006) in 1960
- Autosomal dominant inheritance pattern
- Prevalence estimated to be 1/56,000 (highest estimate)
- Targeted systems affected are the skin, CNS, bones, eyes, and the endocrine system
- Clinical features:
  1. Skin: Multiple BCC’s, pitting of the palms and soles
  2. Skeletal: Hypertelorism, frontal bossing, keratocystic odontogenic tumors (75% of patients), rib and vertebral anomalies, falk cerebri calcification, kyphoscoliosis
  3. Extra-cutaneous tumors: medulloblastoma, fibromas: ovarian and cardiac
  4. Cleft lip and/or palate
IV. **FDA-Approval of Vismodegib and Sonidegib**:

- Vismodegib (Erivedge®) from Genentech (South San Francisco) approved in January 2012
- Sonidegib (Odomzo®) from Novartis (Basel, Switzerland) approved in July 2015
- Mechanism of action: Vismodegib and Sonidegib bind to **SMO** which inhibits **SMO** activation of the **GLI** transcription factors. As mentioned, **SMO** is normally inhibited by **PTCH1**. When **PTCH1** has an inactivating mutation, such as in BCC, it fails to inhibit **SMO**. Vismodegib restores that function by independently inhibiting **SMO** directly.

V. **FDA-Approved Clinical Applications**:

- Vismodegib is approved for the FDA in the following clinical scenarios:
  1. Metastatic BCC (which has an average life-expectancy of 8 years)
  2. Recurrent BCC after surgery and not deemed salvageable by repeat surgery
  3. Locally advanced BCC thought to be inoperable or inappropriate for radiotherapy
- Dosage: 150 mg PO daily
- Cost: $250/capsule = $7500/month

- Sonidegib: approved by the FDA for the following clinical scenarios:
- Indicated for adults with locally advanced basal cell carcinoma (BCC) that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy
- Dosage: 200 mg PO daily
- Cost: $352.35/capsule = $10,570.50/month

VI. **Efficacy Data: Vismodegib and Sonidegib efficacy data are very similar.**

- Vismodegib: Phase 2 Trial for metastatic (mBCC) or locally advanced BCC (laBCC) *(N Engl J Med 2012;366:2171-9)*
  1. N = 104 patients (33 with mBCC, 71 with laBCC)
  2. mBCC: objective response rate = 30%, and 33% at 12 month follow-up (all were partial responses)
    - Median duration of response = 7.6 months (7.6 months @12 month f/u)
    - Progression-free survival = 9.5 mos. (9.5 mos @ 12 month f/u)
  3. laBCC: objective response rate = 43%, and 48% at 12 month follow-up
    - Complete responses = 21%
    - Partial responses = 13%
    - Stable disease = 38%
    - Median duration of response = 7.6 mos. (9.5 mos @ 12 month f/u)
    - Progression-free survival = 9.5 mos. (9.5 mos @ 12 month f/u)
  4. Side-effects: 100% of patients experienced an adverse event (AE)
• The percentage of patients discontinuing treatment due to an AE was 11.5% in the first analysis and increased to 17.3% at the 12-month follow-up
• 57% of AE’s were grade 1 or 2
• 12% had to discontinue the drug due to an AE, (muscle spasm the most common)
• 25% has serious AE’s with 7 deaths (it is not known if the deaths were AE-related)

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• 12-month follow-up update on safety: (Sejulik A et al. J Am Adad Dermatol. 2105; 72(6):1021-6)
• Reasons for discontinuing drug:
  o mBCC: 42% disease progression
    12% patient decision
    12% adverse events
  o lABCC: 28% patient decision
    20% adverse events
    11% disease progression

VII. Managing Side-Effects:
  o The three most common side effects are identical with vismodegib and sonidegib and are thought to be directly related to inhibition of the hedgehog pathway which is involved in the cellular cycling associated with both the hair follicle (alopecia side effect) and the taste cells of the tongue (dysgeusia and aguesia). For this reason, these are side effects that, to date, are very difficult to treat.
    1. Fortunately, the side effects are, for the most part, reversible once the patient stops the drug.
    2. Also, if the patient has not encountered the side effects within the first several months of treatment, they are not likely to develop them with longer term treatment.
To date, the cause of the muscle spasms is unknown. A theory exists that disrupting the Hedgehog pathway may have an effect on calcium channels in cell membranes. There are two strategies that seem to help in some patients:

1. Pickle juice: anecdotally used by athletic trainers to treat athletes’ muscle cramps.
   - A study compared de-ionized water ingestion to pickle juice ingestion after inducing a leg cramp in the flexor hallicus brevis muscle in dehydrated males. *(Med Sci Sports Exerc. 2010 May;42(5):953-61)*
   - There was a statistically significant decrease in the duration of the cramps when subjects ingested pickle juice after cramp induction compared to the placebo.
   - The authors hypothesize that it is the *acetic acid* in pickle juice and not the electrolytes that alleviates cramping.
     a. They postulate that acetic acid stimulates a reflex arc in the oropharynx that stimulates inhibitory neurotransmitters.
     b. In turn, inhibitory neurotransmitters override the muscle contractions.
     c. Our Medical Oncologist, Ken Grossmann, MD, PhD is convinced that pickle juice ingestion does reduce cramping frequency in most patients.

2. Calcium-channel blockade: it has been hypothesized that smoothened inhibition blocks hedgehog signaling but also other types of signaling involving cell membrane calcium channel activation and subsequent muscle spasm.
   - A trial of amlopidine 10 mg/d was given for 8 weeks in patient with basal cell nevus syndrome on vismodegib 150 mg/day. *(JAMA Dermatol. 2015;151(10):1132-1133.)*
   - There was a reduction in the frequency of the cramps but not the severity or duration of the cramps (a reduction of 5.8% per week of treatment)

3. To my knowledge, there has not been a trial combining pickle juice or acetic acid with a calcium channel blocker.

4. Glycine is a potent inhibitory neurotransmitter, therefore, glycine supplementation might be worth investigating. I have no idea if it would work but should be well tolerated.

**VIII. Potential Off-Label Clinical Applications:**

1. Basal Cell Nevus Syndrome (BCNS): Continuous therapy
   - Vismodegib 150 mg/day for 18 months
   - Endpoint: the number BCCs eligible for surgical resection
4. Results:

- 93% completed the first 3 months of treatment
- The number of surgically eligible BCCs was 2 vs. 25 in the vismodegib vs. placebo arms respectively (p<0.001)
- The size of the surgically eligible BCCs decreased significantly from - 65% vs. - 11% in the vismodegib vs placebo arms respectively. (I can’t explain why the tumors in the placebo group also shrunk).
- Adverse events: 54% of participants discontinued vismodegib due to side effects: dysguesia, muscle cramps, alopecia, and weight loss.
- Most surgically eligible BCCs regrew after drug cessation.

  o Basal Cell Nevus Syndrome (BCNS): Intermittent therapy
    1. A letter re. intermittent therapy in BCNS reports on two patients *(JAMA Derm 2015;28:E1-E2)*
    2. Two regimens were used:
      - Patient 1: 1 month on, 2 months off
      - Patient 2: 2 months on, 2 months off
      - The number of BCCs reduced nicely in each patient
      - We have tried a 1 month on, 2 month off regimen in one patient who didn’t tolerate it. His experience is that it took two months before he felt better and was demoralized to have to start the vismodegib again and discontinued his treatment.

  o Patients with multiple BCCs but don’t have BCNS?
    1. ClinicalTrials.gov Identifier: NCT 01815840: Two vismodegib regimens in patients with multiple BCCs (not enrolling)
      - Arm A: 12 weeks of daily vismodegib then 8 weeks placebo
      - Arm B: 24 weeks of daily vismodegib then 8 weeks placebo, then 8 weeks vismodegib
    2. ClinicalTrials.gov Identifier: NCT02067104: Chemoprevention trial (actively enrolling)
      - Arm A: 2 months of daily placebo, 2 months off x 24 months
      - Arm B: 2 months of daily vismodegib, 2 months off x 24 months

IX. **Unanswered Questions/Future Directions:**

We all have patients struggling with multiple BCCs that are caught in a revolving door with the Mohs surgeon. Some had RT for acne as teenagers, most have had a great deal of sun exposure. They greatly outnumber the patients with metastatic BCC, locally advanced BCC, or the Basal Cell Nevus Syndrome combined. How can we best help these patients understanding the following limitations?

  o 54% of BCNS patients discontinued vismodegib due to side effects:
1. Hair loss and taste disruption appear to be consequences of interrupting the Hedgehog pathway, therefore, there is no intervention in the foreseeable future that will lessen those side effects.

2. Muscle spasm may possibly be mitigated by oral acetic acid (pickle juice), calcium channel blockers, glycine supplementation or combination therapy. Clinical trials need to be done to see if these interventions actually work.

   - It is theorized that at least in BCNS patients, most tumors regrow after cessation of therapy leading to the hypothesis that there are cancer stem cells that are temporarily slowed by a smoothened inhibitor but not killed. Is there a second intervention that might help overcome the high recurrence rate?

   - Vismodegib costs $250/capsule, Sonidegib costs $352/capsule. Are third party payers going to cover the cost of these drugs in the off-label setting? Will Genentech or Novartis seek FDA approval for the prophylactic setting?

   - We don’t have data on the neo-adjuvant use of vismodegib followed by Mohs surgery, i.e. it may not shrink the surgical defect at all in terms of the final defect size. It may debulk the tumor but not ultimately reduce the tumor footprint. If that is the case, what value does it have in the neo-adjuvant setting? This is the same question regarding imatinib in the neo-adjuvant setting for recurrent dermatofibrosarcoma protuberans.

   - Following are some clinical trials attempting to answer some of these questions:

     1. Photodynamic therapy combined with vismodegib: ClinicalTrials.gov Identifier: NCT02639117 (not yet recruiting)

     2. Intermittent vismodegib vs. PDT: ClinicalTrials.gov Identifier: NCT01556009 (ongoing, not recruiting)

        - Vismodegib x 7 months, then 3 months on, 3 months off until 28 months
        - Vismodegib x 7 months then discontinue, then PDT at 10 months and every 3 months until 28 months

     3. Vismodegib given to patients based on histologic subtype: ClinicalTrials.gov Identifier: NCT0170049 (currently recruiting)

        - Tumors stratified by histologic subtype: infiltrative/morpheaform, nodular, superficial
        - All patients receive vismodegib daily x 12 weeks then undergo a biopsy
          - Biopsy negative: observation
          - Biopsy positive: continue vismodegib x 12 additional weeks

     4. Vismodegib as neo-adjuvant therapy for BCC followed by Mohs surgery: ClinicalTrials.gov Identifier: NCT01631331 (ongoing, not recruiting)