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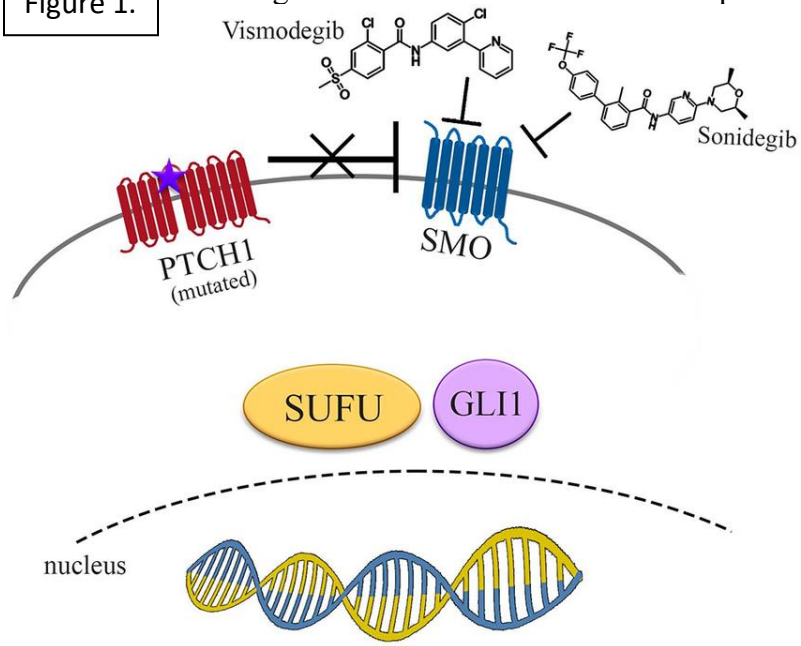
Positive Quality Intervention: Sonidegib (Odomzo®) Patient Management

Description:
The purpose of this PQI is to discuss clinical considerations surrounding the use of sonidegib for adult patients with advanced basal cell carcinoma (BCC).

Background:
Sonidegib is a hedgehog (HH) pathway inhibitor that binds to and inhibits the smoothened homologue (SMO) involved in HH signal transduction.[1] Abnormal activity in the HH pathway related to PTCH1 mutation is associated with development of BCC.[2] Wildtype PTCH1 inactivates SMO upon binding with sonic hedgehog (SHH) ligand. In BCC, PTCH1 is mutated and can no longer inactivate SMO. Hedgehog inhibitors such as sonidegib or vismodegib bind to SMO to inhibit its activity, hence functioning as a wildtype activated PTCH1 (Figure 1).[3]

Figure 1.



Sonidegib is indicated in the treatment of patients with locally advanced BCC (laBCC) that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy.[1] In the multicenter, double-blind, phase 2 BOLT trial, patients with locally advanced, unresectable, or metastatic BCC were randomized (2:1) to receive either sonidegib 800 mg or 200 mg orally, once daily, until disease progression or intolerable toxicity.[2] At a follow-up of 30 months, patients with laBCC achieved an overall response rate (ORR) of 56.1% in the 200 mg arm vs 45.3% in the 800 mg arm.[4] Sonidegib 200 mg had a better safety profile compared to 800 mg, with lower rates of grade 3/4 adverse events (AEs; 43.0% vs. 64.0%) and AEs leading to discontinuation (30.4% vs. 40.0%). The median duration of response was 26.1 months (95% CI:10.1, not reached) (all endpoints assessed by independent central review committee). [4]

In a single center retrospective analysis of 20 BCC patients treated with sonidegib, 9 patients were treated using a modified treatment schedule of every other day dosing to avoid severe AEs.[5] Patients in the dose adjustment group had comparable clinical responses to those on the daily dosing regimen, but experienced fewer AEs overall. In the dose adjustment group, 66.7% (6/9) achieved complete responses, and 33.3% (3/9) had partial responses. All 9 patients experienced only mild (grade 1-2) adverse events, with no severe AEs reported.[5]
In a post hoc analysis comparing sonidegib to vismodegib in advanced BCC, sonidegib-treated patients had a more delayed median time to onset for all AEs than vismodegib-treated patients, except fatigue and weight decrease.[6] In vismodegib-treated patients, most treatment-emergent adverse events occurred within the first two months. After three cycles of vismodegib, muscle spasms, dysgeusia, and alopecia rates were around 60%, 60%, and 25%, respectively. In contrast, the rates for sonidegib were lower, at 32.9%, 15.2%, and 5.1%, respectively. Sonidegib has a longer elimination half-life (30–41 days vs. 4–12 days for vismodegib) and a much larger volume of distribution (>9,000 vs. 26.6L for vismodegib), indicating greater tissue penetration.[1,6,7]

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PQI Process:

- Physicians and advanced practice providers should identify patients who are candidates for sonidegib therapy that have laBCC that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy
- It may be useful to perform next generation sequencing (NGS) focusing on PTCH1 and SMO. Some SMO mutations confer resistance to sonidegib and other SHH ligand inhibitors. In this case, other treatment considerations should be planned.[8]
- Anticancer activity may take as long as 4 months to be assessed, however, some patients respond within 1 month.
- All existing patient prescriptions should be reviewed for any drug interactions with therapy
    - Avoid use with strong CYP3A inhibitors and avoid long-term (greater than 14 days) use of moderate CYP3A inhibitors.
    - Avoid strong and moderate CYP3A inducers.
- Once medication access is secured and an estimated start date is known, schedule patient for medication education session, if not already completed; ensure that patient understands rationale for treatment, expected benefit, how to take medication, and common side effects associated with therapy.

Table 1. Dosing considerations for sonidegib

Dosage form	200 mg capsules
Recommended dosage	200 mg (1 capsule) orally once daily taken on an empty stomach, at least 1 hour before or 2 hours after a meal
Treatment hold or interruption recommended for the following criteria*	• Severe or intolerable musculoskeletal adverse reactions • First occurrence of serum creatine kinase (CK) elevation between 2.5-10x upper limit of normal (ULN). Recurrent serum CK elevation between 2.5-5x ULN
Treatment permanent discontinuation recommended for the following criteria	• Serum CK elevation >2.5 x ULN with worsening renal function • Serum CK elevation >10 x ULN • Recurrent serum CK elevation >5x ULN • Recurrent severe or intolerable musculoskeletal adverse reactions

*Ask if patient has moderately to extensively exercised the day prior to CK measurement, which affects results. Thus, CK must be interpreted in the physiological and clinical context of patient reported activities and symptoms. If holding treatment, sonidegib may be resumed upon resolution of clinical signs and symptoms.

- Potential dosing schedule modifications for patients experiencing toxicities
    - Change frequency from once daily to every other day
    - If toxicities persistent after extending frequency to every other day, attempt three times weekly dosing
    - If no resolution of toxicities, it may be beneficial to interrupt therapy as mentioned above
- Monitoring parameters[1]
    - Obtain serum CK and creatine levels prior to initiating therapy, periodically during treatment, and as clinically indicated
    - Obtain pregnancy test in females of reproductive potential due to embryo-fetal death or severe birth defect associated with sonidegib.
    - Patients should not breastfeed during treatment and for 20 months after their final dose of sonidegib.

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Patient-Centered Activities:[1]

- Provide Oral Chemotherapy Education (OCE) Sheet
- Sonidegib is associated with minimal to low emetic potential; PRN antiemetics may be recommended if patient is experiencing nausea and vomiting.
- Counseling pearls
    - Administration:
        - Swallow capsule whole; do not crush, chew, or split
        - Take on an empty stomach at least 1 hour before or 2 hours after a meal
        - If a dose is missed, skip the missed dose and take next dose as scheduled
        - Avoid grapefruit or grapefruit juice while on therapy
    - Common adverse reactions: muscle spasms, alopecia, dysgeusia, fatigue, nausea, musculoskeletal pain, diarrhea, decreased weight, decreased appetite, myalgia, abdominal pain, headache, pain, vomiting, and pruritus
    - Concomitant use of daily coenzyme Q-10 and calcium carbonate-vitamin D can aid in prevention of muscle spasms.[9] Consider a muscle relaxant if side effects persist. L-carnitine might also be effective but must be taken three times daily and can be expensive.
    - For male patients with female partners, advise to use condoms, even after a vasectomy, during treatment and for at least 8 months after last dose of sonidegib. Do not donate semen while taking sonidegib and for at least 8 months after your final dose.
    - For female patients, advise to use effective contraception during treatment and for at least 20 months after the last dose
    - Advise patients not to donate blood or blood products while taking sonidegib and for 20 months after the last dose

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